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(54) Title: BALANOL ANALOGUES

(57) Abstract

The present invention relates to a solid phase methodology for the preparation of a combinatorial library of structural analogues of the natural product balanol (ophiocordin, azepinostatin), which is a protein kinase C (PKC) and protein kinase A (PKA) inhibitor. The method comprises solid-phase synthesis of the analog variants of balanol whereby a high molecular diversity is introduced. The synthetic scheme is based on a retrosynthetic analysis of the native structure which revealed three main building blocks suitable as templates for modification. The dicarboxy-functional moiety can be immobilised to the polymer support either as the monoallyl ester or as the internal anhydride. The libraries produced by the method are especially suited for high throughput screening of potential drug candidates for the treatment of mammals, especially humans.

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BALANOL ANALOGUES

FIELD OF THE INVENTION

The present invention relates to a novel method for the preparation of balanol analogues using a specially developed combinatorial chemistry scheme. The scheme is also especially suited for the preparation of libraries of balanol analogues. The present invention gives access to novel classes of compounds which may have interesting and unexpected structural and functional features, and, thus, the present invention also relates to the use of the libraries for screening purposes and to the use of novel compounds as medicaments for the treatment of various diseases.

BACKGROUND OF THE INVENTION

In traditional medicinal chemistry, an average of 10,000 different compounds are synthesised and tested during the process of finding the one active component with the right pharmacological and toxicological properties (the drug). The combined experiences from a series of analytical, crystallographic, synthetic organic and computational chemistry techniques have been collected and generated a whole new field often termed "Rational Drug Design". These methods have been expected to speed up and facilitate the search for new lead compounds and drugs, but have so far not proven very effective. Today the average cost for a new drug still runs around US$ 250-350,000,000 and it takes an average of 12 years for a new drug to reach the market place. Furthermore, in spite of obvious scientific progress during the last couple of decades, many diseases are still threatening mankind because of no or insufficient treatment. These obviously include AIDS, cardiovascular diseases and human cancers but also diseases related to neuro-degenerative disorders (e.g. Alzheimer's disease), metabolic disorders (Type 2 Diabetes) and other diseases affecting not only the quantity but also the quality of life.

To facilitate this search for novel biologically active compounds, a new chemical/analytical technique has emerged. This research area is often termed combinatorial chemistry and it is one of the fastest growing research areas in modern organic chemistry. The synthesis and screening of vast and diverse libraries of small molecules might lead not only to new drugs but might also have a great importance for the discovery of novel synthetic receptors, new materials or new catalysts. Most of the reported literature in this field have been concerned with libraries consisting of small peptides and oligonucleotides because synthetic protocols for solid-phase synthesis of these molecules have been optimised for decades. However, small molecules represent a larger challenge for the synthetic organic chemist as well hold the potential for finding possible leads for the drug discovery process.

The generation of chemical diversity using combinatorial chemistry is one of the most active fields of modern organic chemistry. Initially, research was focused on the generation on peptide and nucleotide libraries but more recently - due to the dubious drug-potential for finding molecules with activities in other areas such as anesthetics, central nervous system depressants such as sedative-hypnotics, anticonvulsants, neuroleptics and anxiolytic agents, drugs to treat neuromuscular disorders such as antiperkinsonism agents or skeletal muscle relaxants, analgesics, central nervous system stimulants, local anesthetics, cholinergic agonists, acetylcholinesterase inhibitors or cholinergic antagonists, adrenergic drugs, cardiac agents such as cardiac glycosides, antianginals, and antiarrhythmic drugs, anticoagulants, coagulants, and plasma extenders, diuretics, antiallergic and antiulcer drugs, antilipidemic drugs, nonsteroidal anti-inflammatory drugs, drugs affecting sugar metabolism, antimycobacterial agents, antibiotics or antimicrobial agents, antifungal agents, as pesticides, antiseptics or disinfectants, as hormone antagonists, antineoplastic agents for cancer chemotherapy or photochemotherapy, antiviral agents or as a potential drugs against HIV-infections and AIDS - the generation of non-peptidic small molecule libraries have attracted most of the attention and resources in this field.

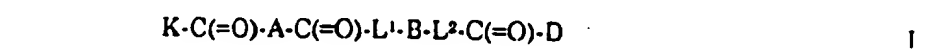
Protein kinase C (PKC) belongs to a family of serine/threonine specific kinases which are involved in a variety of processes including signal transduction, cell proliferation and cell differentiation. Agents that inhibit PKC may have wide ranging therapeutic potential, since activated PKC has been implicated in numerous disease processes. These include some widespread and severe diseases such as cancer, inflammation, cardiovascular dysfunctions, diabetic complications, asthma, central nervous system disorders and HIV infection.

Balanol is a fungal metabolite, which has attracted significant attention because it possesses high PKC inhibiting activity. Furthermore, balanol has a relatively favourable therapeutic index compared to staurosporin, which is another known PKC inhibitor. The literature contains several examples of total syntheses of balanol in solution (Lampe, J.W.; Hughes, P.F.; Bigger, C.K.; Smith, S.H.; Hu, H. *J. Org. Chem.* **1994**, 59, 5147-5148; Lampe, J.W.; Hughes, P.F.; Bigger, C.K.; Smith, S.H.; Hu, H. *J. Org. Chem.* **1996**, 61, 4572-4581; Nicolaou, K.C.; Bunnage, M.E.; Koide, K.J. *J. Am. Chem. Soc.* **1994**, 116, 8402-8403; Adams, C.P.; Fairway, S.M.; Hardy, C.J.; Hibbs, D.E.; Hursthouse, M.B., Morley, A.D.; Sharp, B.W.; Vicker, N.; Warner, I. *J. Chem. Soc. Perkin Trans. I*, **1995**, 2355-2362) and some analogues with improved selectivity (Lai, Y.-S.; Stamper, M. *Bioorg. Med. Chem. Lett.* **1995**, 5, 2147-2150; Lai, Y.-S.; Menaldino, D. S.; Nichols, J. B.; Jagdmann, G. E. J.; Mylott, F.; Gillespie, J.; Hall, S. E. *Bioorg. Med. Chem. Lett.* **1995**, 5, 2151-2154; Nicolaou, K. C.; Koide, K.; Bunnage, M. E. *Chem. Eur. J.* **1995**, 1, 454-466). However, all these syntheses involve numerous synthetic steps and a level of complication in th applied chemistry that is not compatible with solid-phase organic synthesis and c mbinatorial chemistry.

SUMMARY OF THE INVENTION

The aim of the present invention is to provide a simplified synthetic scheme for the preparation of balanol analogues using solid-phase synthesis methodologies. It is believed that a novel solid phase method for the preparation of balanol analogues may provide easier access to known analogues and also provide hitherto unknown balanol analogues. The synthetic scheme will also allow for the easy preparation of combinatorial libraries of balanol analogues.

Thus, the present invention provides a method for the preparation of balanol derivatives of the following general formula I:



wherein K-C(=O)- designates a carboxy group or a derivative thereof; each of A and B designates an organic biradical; each of L^1 and L^2 independently designates -NR^5- or -O-, wherein each R^5 independently is selected from hydrogen, optionally substituted C_{1-20}-alkyl, optionally substituted C_{1-20}-alkenyl, optionally substituted C_{1-20}-alkadienyl, optionally substituted C_{1-20}-alkatrienyl, optionally substituted aryl, and optionally substituted heteroaryl, or R^3 designates an additional bond to B (whereby B becomes a triradical); and D designates optionally substituted aryl or optionally substituted heteroaryl; the method comprises the following steps:

(A) providing an optionally functional group protected moiety -C(=O)-A-C(=O)-M^1 immobilised to a solid support material, wherein -C(=O)-M^1 designates a carboxy group or a derivative thereof;

(B) coupling an optionally functional group protected difunctional entity L'^1-B-L'^2 to the -C(=O)-M^1 end of the immobilised moiety -C(=O)-A-C(=O)-M^1 for the formation of an optionally functional group protected immobilised fragment -C(=O)-A-C(=O)-L^1-B-L'^2;

(C) coupling an optionally functional group protected entity D-C(=O)-M^2, wherein C(=O)-M^2 designates a carboxy group or a derivative thereof, to the L'^2 end of the immobilised fragment -C(=O)-A-C(=O)-L^1-B-L'^2 for the formation of an optionally functional group protected immobilised compound -C(=O)-A-C(=O)-L^1-B-L^2-C(=O)-D, the step optionally including deprotection of any protection group involved in L'^2; and

(D) cleaving the compound K-C(=O)-A-C(=O)-L^1-B-L^2-C(=O)-D from the solid support material, the step optionally including deprotection of one or more functional group(s) attached to A, B, and/or D.

The present invention also provides a method for the preparation of a multi-dimensional array of compounds, {A}-{B}-{D}, consisting of at least four compounds, preferably in the range of 6-200 compounds, more preferably in the range of 6-100 compounds, in particular in the range of 8-64 compounds each having the general formula I as defined above, comprising the following steps:

(A) providing an array {A} of m optionally functional group protected moieties -C(=O)-A-C(=O)-M^1 immobilised to a solid support material, wherein -C(=O)-M^1 designates a carboxy group or a derivative thereof;

(B) coupling an array {B} of n optionally functional group protected difunctional entities L'^1-B-L'^2 to the -C(=O)-M^1 end of the immobilised moieties -C(=O)-A-C(=O)-M^1 for the formation of an array {A}-{B} of m•n optionally functional group protected immobilised fragments -C(=O)-A-C(=O)-L'^1-B-L'^2;

(C) coupling an array {D} of o optionally functional group protected entities D-C(=O)-M^2, wherein -C(=O)-M^2 designates a carboxy group or a derivative thereof, to the L'^2 end of the immobilised fragments -C(=O)-A-C(=O)-L'^1-B-L'^2 for the formation of an array {A}-{B}-{D} of m•n•o optionally functional group protected immobilised compounds -C(=O)-A-C(=O)-L'^1-B-L^2-C(=O)-D, the step optionally including deprotection of any protection group involved in L'^2; and

(D) cleaving the array {A}-{B}-{D} of compounds K-C(=O)-A-C(=O)-L^1-B-L^2-C(=O)-D from the solid support material, the step optionally including deprotection of one or more functional group(s) attached to individual As, Bs, and/or Ds.

Some of the novel analogues should not at first sight be expected to have any biological effects since they are structurally quite distinct from the original balanol molecule, however it is believed that such compounds may be useful as medicaments in that they are expected to have a higher specificity than balanol itself.

Thus, the present invention also provides the use a compound library for screening purposes and the use of individual compound as a medicament.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

In the present context, the term "C_{1-20}-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 20 carbon atoms, such as methyl, ethyl, propyl, iso-propyl,

cyclopropyl, butyl, *tert*-butyl, iso-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, cyclohexyl, hexadecyl, heptadecyl, octadecyl, nonadecyl. Analogously, the term "C_{1-6}-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, iso-propyl, pentyl, cyclopentyl, hexyl, cyclohexyl, and the term "C_{1-4}-alkyl" is intended to cover linear, cyclic or branched hydrocarbon groups having 1 to 4 carbon atoms, e.g. methyl, ethyl, propyl, iso-propyl, cyclopropyl, butyl, *iso*-butyl, *tert*-butyl, cyclobutyl.

Preferred examples of "C_{1-6}-alkyl" are methyl, ethyl, propyl, iso-propyl, butyl, *tert*-butyl, iso-butyl, pentyl, cyclopentyl, hexyl, cyclohexyl, in particular methyl, ethyl, propyl, iso-propyl, *tert*-butyl, iso-butyl and cyclohexyl. Preferred examples of "C_{1-4}-alkyl" are methyl, ethyl, propyl, iso-propyl, butyl, *tert*-butyl, and iso-butyl.

Similarly, the terms "C_{2-20}-alkenyl", "C_{4-20}-alkadienyl", and "C_{6-20}-alkatrienyl" are intended to mean a linear, cyclic or branched hydrocarbon group having 2 to 20, 4 to 20, and 6 to 20, carbon atoms, respectively, and comprising one, two, and three unsaturated bonds, respectively. Examples of alkenyl groups are vinyl, allyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, heptadecaenyl. Examples of alkadienyl groups are butadienyl, pentadienyl, hexadienyl, heptadienyl, heptadecadienyl. Examples of alkatrienyl groups are hexatrienyl, heptatrienyl, octatrienyl, and heptadecatrienyl. Preferred examples of alkenyl are vinyl, allyl, butenyl, especially allyl.

Similarly, the term "C_{2-20}-alkynyl" is intended to mean a linear or branched hydrocarbon group having 2 to 20 carbon atoms and comprising a triple bond. Examples hereof are ethynyl, propynyl, butynyl, octynyl, and dodecaynyl.

In the present context, i.e. in connection with the terms "alkyl", "alkenyl", "alkadienyl", "alkatrienyl", and "alkynyl", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-3 times, with group(s) selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C_{1-6}-alkoxy (i.e. alkyl-oxy), C_{2-6}-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, arylcarbonyl, heteroaryl, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, C_{1-6}-alkanoyloxy, sulphono, C_{1-6}-alkylsulphonyloxy, nitro, sulphanyl, C_{1-6}-alkylthio, trihalogen-C_{1-4}-alkyl, halogen such as fluoro, chloro, bromo or iodo, where aryl and heteroaryl may be substituted as specifically describe above for "optionally substituted aryl and heteroaryl".

Preferably, the substituents are selected from hydroxy, C_{1-6}-alkoxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, arylcarbonyl, heteroaryl, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, carbamido, trihalogen-C_{1-4}-alkyl, halogen such as fluoro, chloro, bromo or iodo, where aryl and heteroaryl may be substituted 1-5 times, preferably 1-3 times, with C_{1-4}-alkyl, C_{1-4}-alkoxy, nitro, amino or halogen. Especially preferred examples are hydroxy, C_{1-6}-alkoxy, carboxy, aryl, heteroaryl, amino, mono- and di(C_{1-6}-alkyl)amino, and halogen such as fluoro, chloro, bromo or iodo, where aryl and heteroaryl may be substituted 1-3 times with C_{1-4}-alkyl, C_{1-4}-alkoxy, nitro, amino or halogen.

In the present context the term "aryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system, such as phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, anthracyl, phenanthracyl, pyrenyl, benzopyrenyl, fluorenyl and xanthenyl, among which phenyl is a preferred example.

The term "heteroaryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or -NR^5-, where R^5 is selected from hydrogen and C_{1-4}-alkyl), sulphur, and/or oxygen atoms. Examples of such heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl, piperidinyl, coumaryl, furyl, quinolyl, benzothiazolyl, benzotriazolyl, benzodiazolyl, benzooxozolyl, phthalazinyl, phthalanyl, triazolyl, tetrazolyl, isoquinolyl, acridinyl, carbazolyl, dibenzazepinyl, indolyl, benzopyrazolyl, phenoxazonyl. Preferred heteroaryl groups are pyridinyl, benzopyrazolyl, and imidazolyl.

In the present context the term "non-aromatic carbocyclic and heterocyclic group" is intended to cover rings comprising carbon atoms only (carbocyclic) or carbon atoms together with heteroatoms (heterocyclic), respectively. Heteroatoms are typically selected from nitrogen, oxygen, and sulphur. Such groups involve no unsaturated bonds or one or several unsaturated bonds, however, if present, situated in such a way that no aromatic π-electron system arises. It should be understood that the radical positions are situated directly on the ring in case of a biradical arising from such a group.

Specific examples of non-aromatic carbocyclic and heterocyclic groups are oxazetane, diazetane, thiazetane, oxazolane, imidazolidine, thiazolane, oxazilane, hexahydropyridazine, thiazilane, oxazepane, diazepane, thiazepane, oxazocane, diazocane, thiazocane, tetrahydrofuran, dihydrofuran, pyrrolidine, tetrahydrothiophen, tetrahydropyran, piperidine, tetrahydrothiopyran, oxepane, azepane, thiepane, oxocane, azocane, thiocane, cyclopropane, oxirane, aziridine,

cyclopropene, azirine, cyclobutane, oxetane, azetidine, thietane, 2-azetidinone, 1,3-lactone, pyrolidine, pyroline, pyrrole, cyclopentene, cyclopentadiene, pyrollidione, pyrollidone, cyclohexyl, oxirane, dioxirane, morpholine, piperidine, 1,5-lactone, 1,5-lactam, cyclohexene, cyclohexadiene, piperidione, tropane, 1,6-lactone (tropolone), 1,6-lactam, azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine. Especially preferred examples are oxirane, aziridine, azirine, oxetane, 2-azetidinone, 1,3-lactone, pyrolidine, pyroline, pyrrole, pyrollidone, pyrollidione, oxirane, dioxirane, morpholine, piperidine, δ-valerolactam (2-piperidone), 1,5-lactone, piperidione, tropolone, 1,6-lactam, azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine. Particularly preferred examples are 2-azetidinone, 1,3-lactone, pyrollidone, 1,5-lactam, 1,5-lactone, tropolone, 1,6-lactam, azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine.

In the present context, i.e. in connection with the terms "aryl", "heteroaryl", and "non-aromatic carbocyclic and heterocyclic group", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times) with group(s) selected from hydroxy (which when present in an enol system may be represented in the tautomeric keto form), C_{1-6}-alkyl, C_{1-6}-alkoxy, oxo (which may be represented in the tautomeric enol form), carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxy, aryloxycarbonyl, arylcarbonyl, heteroaryl, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)-amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, C_{1-6}-alkanoyloxy, sulphono, C_{1-6}-alkylsulphonyloxy, nitro, sulphanyl, dihalogen-C_{1-4}-alkyl, trihalogen-C_{1-4}-alkyl, halogen such as fluoro, chloro, bromo or iodo, where aryl and heteroaryl representing substituents may be . Preferred examples are hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, aryl, amino, mono- and di(C_{1-6}-alkyl)amino, and halogen such as fluoro, chloro, bromo or iodo, wherein aryl and heteroaryl may be substituted as above.

In the present context the synonymous terms "organic biradical" and "biradical" are intended to have the meaning normally associated therewith. Thus, such biradicals may be derived from practically any organic molecule from which two (non-geminal and theoretical) hydrogen atoms are removed. In the present context, interesting biradicals are either linear or cyclic or comprises two or more domains selected from linear and cyclic sub-biradicals. Illustrative examples of combined biradicals comprising domains which have both linear and cyclic character are phenylene-carbonyl-phenylene, methylene-phenylene-methyleneoxy, and methylene-phenylene.

Examples of linear biradicals or domains of a combined biradical are 1-20 carbon atom alkylene chain optionally interrupted and/or terminated by one or more heteroatoms selected from O, S, and NR^5, and optionally substituted one or several times, preferably 1-5 times, in particular 1-3 times, with substituent(s) selected from optionally substituted C_{1-6}-alkyl, optionally substituted

C_{2-6}-alkenyl, optionally substituted C_{4-6}-alkadienyl, optionally substituted C_{6-8}-alkatrienyl, hydroxy, oxo (thereby forming a keto or aldehyde functionality), -O-R^6, formyl, -C(=O)-R^6, -O-C(=O)-R^6, carboxy, -C(=O)-O-R^6, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted aryl, optionally substituted aryloxy, halogen such as fluoro, chloro, bromo, and iodo, nitro, cyano, -$N(R^5)_2$, -$N(R^7)$-CO-R^6, carbamoyl, mono- or di(C_{1-6}-alkyl)-aminocarbonyl, sulphanyl, optionally substituted C_{1-6}-alkylthio, optionally substituted C_{1-6}-alkyl-thio-C_{1-6}-alkyl, (optionally substituted aryl)thio, guanidino, sulphono (-SO_3H), sulphino (-SO_2H), halosulphonyl, -$OS(O)_m$-R^6 where m is 2 or 3, -$N(R^7)S(O)_m$-R^6 where m is 2 or 3, -$S(O)_m$-$N(R^7)_2$ where m is 2 or 3, -$S(O)_m$-NH(R^7) where m is 2 or 3, -$S(O)_m$-NH_2 where m is 2 or 3, isocyano, isothiocyano, thiocyano, -$OP(O)_p(R^6)_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5, and -$N(R^7)P(O)_p(R^6)_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5; wherein each R^5 and each R^6 independently is selected from hydrogen, optionally substituted C_{1-20}-alkyl, optionally substituted C_{2-20}-alkenyl, optionally substituted C_{4-20}-alkadienyl, optionally substituted C_{6-20}-alkatrienyl, optionally substituted aryl, and optionally substituted heteroaryl; and each R^7 is selected from hydrogen and C_{1-4}-alkyl.

Especially preferred examples of linear biradicals or domains of a combined biradical are substituents are 1-6 carbon atom alkylene chain optionally interrupted and/or terminated by one or two heteroatoms selected from O, S, and NR^5, and optionally substituted 1-3 times with substituent(s) selected from optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, hydroxy, oxo (thereby forming a keto or aldehyde functionality), -O-R^6, formyl, -C(=O)-R^6, -O-C(=O)-R^6, carboxy, -C(=O)-O-R^6, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted aryl, optionally substituted aryloxy, halogen such as fluoro, chloro, bromo, and iodo, cyano, -$N(R^5)_2$, -$N(R^7)$-CO-R^6, carbamoyl, mono- or di(C_{1-6}-alkyl)amino-carbonyl, C_{1-6}-alkylthio, wherein each R^5 and R^7 independently is selected from hydrogen and C_{1-4}-alkyl, and each R^6 independently is selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted aryl, and optionally substituted heteroaryl.

The biradical may also consist of or comprise one or more cyclic elements, in particular 5- or 6-or 7-membered cyclic elements. Each such cyclic element may independently be saturated, unsaturated or fully or partially aromatic; it may be carbocyclic, or it may be heterocyclic by incorporating 1, 2, 3, or 4 heteroatoms, typically selected from nitrogen (=N- or -NR^5-, where R^5 is as defined above for the linear biradicals), oxygen or sulphur. In the case of several cyclic elements being present, these may be connected through single or double bonds, or they may be fused, or combinations thereof.

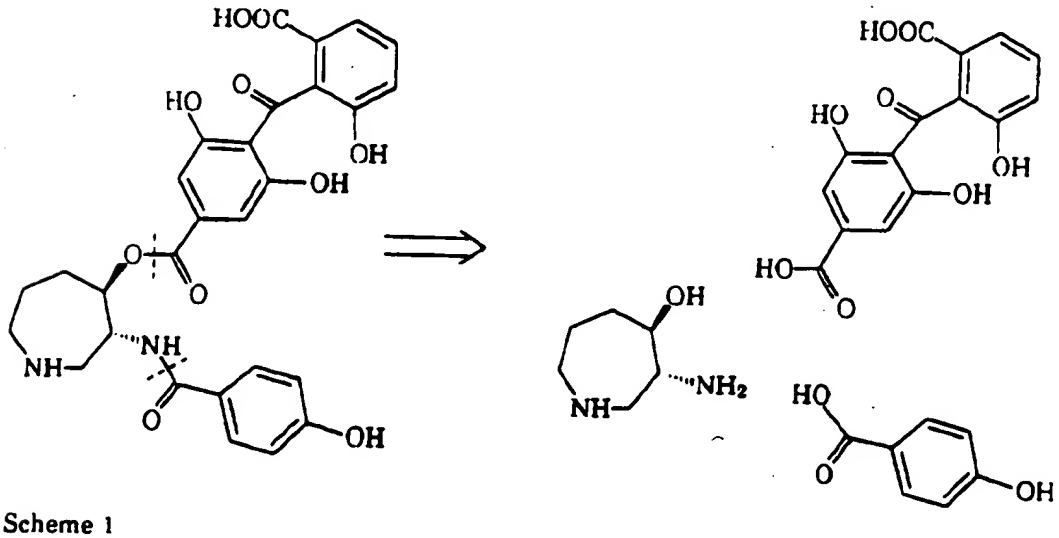
Examples of cyclic biradicals are biradicals of optionally substituted aryl groups and optionally substituted heteroaryl groups as well as biradicals of optionally substituted non-aromatic carbocyclic and heterocyclic groups.

As it will be evident from the general formula I and the definitions associated therewith, there may be one or several asymmetric carbon atoms present in the compound I depending on the nature of the biradicals and the possible substituents, cf. below. The compounds prepared according to the method of the invention, as well as the compound I per se, are intended to include all stereoisomers arising from the presence of any and all isomers of the individual moieties as well as mixtures thereof, including racemic mixtures.

It should furthermore be understood that the compounds of the general formula I include possible salts thereof, of which pharmaceutically acceptable salts are especially relevant. Salts include acid addition salts and basic salts. Examples hereof are hydrochloride salts, sodium salts, calcium salts, potassium salts, etc.. Pharmaceutically acceptable salts are, e.g., those described in Remington's Pharmaceutical Sciences, 17. Ed. Alfonso R.Gennaro (Ed.), Mack Publishing Company, Easton, PA, U.S.A., 1985. Furthermore, final products may also be present in hydrate form.

Construction of the compounds of the general formula I

The rationale for the method according to invention is illustrated in Scheme 1, where a retrosynthetic analysis of balanol lead to the identification of three main building blocks or synthons which are mono-protected aromatic diacids, aminoalcohols and benzoic acid derivatives, respectively.



Scheme 1

Thus, with reference Scheme 1, a number of modification are possible and also realistic within the scope of the present invention. For example, the balanol molecule comprises one amide bond and one ester bond, corresponding to -L^2-C(=O)- and -C(=O)-L^1-, respectively. However, the analogues which are possible within the present invention may comprise two amide bond or two ester bonds, or the bonds may be interchanged, so that the ester bond corresponds to -L^2-C(=O)- and the amide bond corresponds to -C(=O)-L^1-. It is furthermore believed that the benzoic acid building block may be represented by any aromatic and heteroaromatic carboxylic acid, and that the diacid may be any other dicarboxylic acid of linear, cyclic, non-aromatic or aromatic origin.

The moiety K-C(=O)- in the general formula I designates a carboxylic acid (K=OH) or a derivative thereof. It should be understood that any of the carboxylic acid derivatives known in the art are possible within the definition of the present invention. However, since the moiety -C(=O)-K arises when cleaving the compound I from a solid phase resin (when the compound I is prepared according to the present invention), the moiety is typically in the free acid form (-COOH; K=OH) or in the carboxylate form (-COO^-; K=O^-), where the counter ion is selected from alkali metals, such as sodium and potassium, alkaline earth metals, such as calcium, and ammonium ions ($N(R)_2R'$), or is derivatised as the amide (-$CONH_2$, -CONHR, -CONRR'; K= NH_2, NHR, NRR', respectively), the hydroxylamide (-CON(OH)H; K=N(OH)H), the hydrazide (-$CONHNH_2$, CONHNHR'''; K= $NHNH_2$, NHNHR''', respectively) or the ester (-COOR''; K=R''), where each of R, R', R'', and R''' independently designates optionally substituted C_{1-20}-alkyl, optionally substituted C_{2-20}-alkenyl, optionally substituted C_{4-20}-alkadienyl, optionally substituted C_{6-20}-alkatrienyl, optionally substituted aryl, or optionally substituted heteroaryl. Furthermore, the C-terminal carboxylic acid may be reduced to the corresponding the corresponding aldehyde (K=H) in the cleavage step. Preferably, K designates OH, O^-, OR'', NH_2, NHR, or NRR', in particular OH, methoxy, or NH_2, where R and R' are selected from C_{1-6}-alkyl and benzyl, and R'' is selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, phenyl, and benzyl.

With respect to the biradical A, this may be an aliphatic biradical of the formula

$$-(CR^3R^4)_n-$$

(i.e. an alkylene chain with no interrupting or terminating heteroatoms)
wherein n is 1-20, preferably 1-12, in particular 2-8, and

where each of R^3 and R^4 independently is selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted C_{4-6}-alkadienyl, optionally substituted C_{6-8}-alkatrienyl, hydroxy, oxo (thereby forming a keto or aldehyde functionality), -O-R^6, formyl, -C(=O)-R^6, -O-C(=O)-R^6, carboxy, -C(=O)-O-R^6, optionally substituted heteroaryl,

optionally substituted heteroaryloxy, optionally substituted aryl, optionally substituted aryloxy, halogen such as fluoro, chloro, bromo, and iodo, nitro, cyano, $-N(R^6)_2$, $-N(R^7)-CO-R^6$, carbamoyl, mono- or di(C_{1-6}-alkyl)aminocarbonyl, sulphanyl, optionally substituted C_{1-6}-alkylthio, optionally substituted C_{1-6}-alkylthio-C_{1-6}-alkyl, (optionally substituted aryl)thio, guanidino, sulphono ($-SO_3H$), sulphino ($-SO_2H$), halosulphonyl, $-OS(O)_m-R^6$ where m is 2 or 3, $-N(R^7)S(O)_m-R^6$ where m is 2 or 3, $-S(O)_m-N(R^7)_2$ where m is 2 or 3, $-S(O)_m-NH(R^7)$ where m is 2 or 3, $-S(O)_m-NH_2$ where m is 2 or 3, isocyano, isothiocyano, thiocyano, $-OP(O)_p(R^6)_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5, and $-N(R^7)P(O)_p(R^6)_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5; wherein each R^5 and each R^6 independently is selected from hydrogen, optionally substituted C_{1-20}-alkyl, optionally substituted C_{2-20}-alkenyl, optionally substituted C_{4-20}-alkadienyl, optionally substituted C_{6-20}-alkatrienyl, optionally substituted aryl, and optionally substituted heteroaryl; and each R^7 is selected from hydrogen and C_{1-4}-alkyl; where at the most 5, preferably at the most 3, of the substituents R^3 and R^4 are different from hydrogen.

The substituents R^3 and R^4 are preferably independently selected from optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, hydroxy, oxo (thereby forming a keto or aldehyde functionality), $-O-R^6$, formyl, $-C(=O)-R^6$, $-O-C(=O)-R^6$, carboxy, $-C(=O)-O-R^6$, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted aryl, optionally substituted aryloxy, halogen such as fluoro, chloro, bromo, and iodo, cyano, $-N(R^6)_2$, $-N(R^7)-CO-R^6$, carbamoyl, mono- or di(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkylthio, wherein each R^5 and R^7 independently is selected from hydrogen and C_{1-4}-alkyl, and each R^6 independently is selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted aryl, and optionally substituted heteroaryl.

Alternatively, the biradical A, illustrated as the fragment $-C(=O)-A-C(=O)-$, could be derived from an aliphatic or aromatic dicarbonyl functionalised moiety, e.g., as illustrated in Figure 1 and 2, wherein X is selected from the group consisting of $>NR^5$, >NH, -O-, -S-, -Se-, -Te-, $-CR^1R^2-$, >C=O, >C=S, and Y^1, Y^2, R^1, and R^2 each independently designate substituents as defined as optional substituent for aryl and heteroaryl (see above); or Y^1 together with Y^2 may form a biradical which together with the atoms located between these substituents, form(s) a 4-, 5-, 6-, 7- or 8-membered ring which may be an optionally substituted non-aromatic carbocyclic or heteroaromatic ring or an optionally substituted aromatic or heteroaromatic rings; and each Z^1 and Z^2 independently designates $=N-$, $=N^+R^5-$;

Preferred examples of the biradical A are biradicals either comprising or consisting of cyclic biradicals of the following radicals: phenyl, naphthyl, anthracyl, pyrenyl, benzopyrenyl, phenoxazonyl, N^8-phenoxazonyl, quinolyl, benzophenazinyl, ethidium and fluorenyl. Especially preferred examples are naphthyl, benzopyrenyl, phenoxazonyl, N^8-phenoxazonyl, quinolyl, benzophenazinyl, ethidium and fluorenyl; and/or comprising or consisting of linear biradicals of

the formula $-(CR^3R^4)_n-$, where each of R^3 and R^4 independently are selected from optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, hydroxy, oxo (thereby forming a keto or aldehyde functionality), $-O-R^6$, formyl, $-C(=O)-R^6$, $-O-C(=O)-R^6$, carboxy, $-C(=O)-O-R^6$, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted aryl, optionally substituted aryloxy, halogen such as fluoro, chloro, bromo, and iodo, cyano, $-N(R^5)_2$, $-N(R^7)-CO-R^6$, carbamoyl, mono- or di(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkylthio, sulphono ($-SO_3H$), sulphino ($-SO_2H$), wherein each R^5 and R^7 independently is selected from hydrogen and C_{1-4}-alkyl, and each R^6 independently is selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted aryl, and optionally substituted heteroaryl.

These aromatic and heteroaromatic biradicals, A, may be substituted with one or more groups selected from the same groups as defined above as substituents for the aryl and heteroaryl groups.

With respect to the carbonyl groups neighbouring A in formula I, it should be understood that these carbonyl groups may be an integral part of a starting material for the preparation of the compound I or libraries of the compound I. Thus, in most cases, it is advantageous to use, as a starting material, a cyclic entity carrying two carboxylic acid groups, one of these groups optionally in protected form, and the other group in the free acid form or in activated form, or alternatively the two carboxy groups in internal anhydride form. In this way, A may easily be linked to the solid phase material.

Illustrative examples of dicarboxylic acid functional compounds, which after incorporation into the compound I will represent the fragment $-C(=O)-A-C(=O)-$, are:

Aromatic and heteroaromatic:
2,2'-biquinoline-4,4'-dicarboxylic acid; 5-nitro-isophthalic acid; 2-amino-terephthalic acid; 2-bromo-terephthalic acid; 2-nitro-terephthalic acid; 3,6-dichloro-phthalic acid anhydride; 4,5-dichloro-phthalic acid anhydride; 3-nitro-phthalic acid anhydride; 4-nitro-phthalic acid anhydride; homophthalic acid; 4,4'-biphenyl-dicarboxylic acid; 2,2'-biphenyl-dicarboxylic acid, 2,3-naphthalene-dicarboxylic acid; 2,6-naphthalene-dicarboxylic acid; 1,8-naphthalene-dicarboxylic acid anhydride; 3-nitro-1,8-naphthalene-dicarboxylic acid anhydride, 1,2-phenylendioxy-diacetic acid; embonic acid; 5,5'-dithiobis-(2-nitrobenzoic acid)(3,3'-6); 2,2'-dithiobenzoic acid; glutamic acic-5-(3-carboxy-4-nitro-anilide); alizarin-3-methyliminodiacetic acid; 1,4-phenylene-diacetic acid; 2,4'-benzophenone-dicarboxylic acid; 2,4'-benzophenyl-dicarboxylic acid; chelidamic acid; 2,3-pyridine-dicarboxylic acid; 2,4-pyridine-dicarboxylic acid; 2,5-pyridine-dicarboxylic acid; 2,6-pyridine-dicarboxylic acid; 3,4-pyridine-dicarboxylic acid; 3,5-pyridine-dicarboxylic acid; 4,5-pyridine-dicarboxylic acid; imidazole-4,5-dicarboxylic acid; 3,4,5,6-tetra-

chloro-phthalic acid; 2-amino-4,6-pyrimidine-dicarboxylic acid; 9,10-anthracene-dicarboxylic acid; 1,4-dihydroxy-naphthalene-2,3-dicarboxylic acid; benzimidazol-5,6-dicarboxylic acid; benzophenone-4,4'-dicarboxylic acid; 4-methoxy-phthalic acid; naphtidine-3,3'-dicarboxylic acid; naphthalene-1,2-dicarboxylic acid; naphthalene-1,3-dicarboxylic acid; naphthalene-1,4-dicarboxylic acid; naphthalene-1,5-dicarboxylic acid; naphthalene-1,6-dicarboxylic acid; naphthalene-1,7-dicarboxylic acid; naphthalene-1,8-dicarboxylic acid; naphthalene-2,3-dicarboxylic acid; naphthalene-2,4-dicarboxylic acid; naphthalene-2,5-dicarboxylic acid; naphthalene-2,7-dicarboxylic acid; naphthalene-2,8-dicarboxylic acid; pyrimidine-4,6-dicarboxylic acid; pyrrazole-3,6-dicarboxylic acid; and 1,10-phenanthroline-5,6-dicarboxylic acid; especially preferred examples are phthalic acid, isophthalic acid, terphthalic acid, 5-nitro-isophthalic acid, 2,6-naphthalene dicarboxylic acid, 1,2-naphthalene dicarboxylic acid, 2,3-naphthalene dicarboxylic acid, biphenyl-4,4'-dicarboxylic acid, biphenyl-2,4'-dicarboxylic acid, 4-methoxy-biphenyl-2,4'-dicarboxylic acid, 2,2'-benzophenonedicarboxylic acid, 3,3'-benzophenonedicarboxylic acid, 4,4'-benzophenonedicarboxylic acid. Benzophenone-2,4'-dicarboxylic acid, 2-methoxy-benzophenone-2'-5-dicarboxylic acid, 2-methoxy-benzophenone-4'-5-dicarboxylic acid 6,2',6'-trihydroxy-2,4'-dicarboxy-bisphenylmethane, 1,1-(6',2'',6''-trihydroxy-2',4''-dicarboxy-diphenyl)-ethene, 6,2',6'-trihydroxybenzophenone-2,4'-dicarboxylic acid, 6,2',6'-trimethoxy-benzophenone-2,4'-dicarboxylic acid, 2-carboxamido-6,2',6'-trihydroxybenzophenone-4'-carboxylic acid, 2-carboxyethyl-6,2',6'-trihydroxybenzophenone-4'-carboxylic acid, 2-carboxymethyl-6,2',6'-trihydroxybenzophenone-4'-carboxylic acid, 6,2',6'-trifluorobenzophenone-2,4'-dicarboxylic acid, 2',6'-dimethoxy-6-hydroxybenzophenone-2,4'-dicarboxylic acid.

and

Linear and non-aromatic:

oxalic acid; malonic acid; succinic acid; glutaric acid; adipic acid; pimelic acid; suberic acid; azelaic acid; sebacic acid; undecanedioic acid; dodecanedioic acid; tetradecanedioic acid; hexadecanedioic acid docosanedioic acid; trans,trans-muconic acid; methylmaleic acid; methylmaleic acid anhydride; (+)- and (-)-camphoric acid; 1,3-acetone dicarboxylic acid; N-(acetamido)-iminodiacetic acid; L-aspartic acid; S-carboxymethyl-L-cysteine; 2,2'-(ethylendithio)-diacetic acid; malic acid (+ and -); D-penicillamine; phenylsuccinic acid; N-(phosphonomethyl)-iminodiacetic acid; tetrahydrofolic acid; (+ or -) O,O'-dibenzyl-2-tartaric acid; (3-thienyl)-malonic acid; N-phtaloyl-l-glutamic acid; diphenyl maleic anhydride; cis-1,2,3,6-tetrahydrophthalic acid; 3,4,5,6-tetrahydrophthalic acid; pyrazine-2,3-dicarboxylic acid; ticarcillin; chelidonic acid; glycine cresol red; cyclopropane-1,1'-dicarboxylic acid; cyclobutane-1,1'-dicarboxylic acid; 1-cyclopentene-1,2-dicarboxylic acid anhydride; 1,1'-azobis-(cyclohexane-carboxylic acid); cyclopropane-1,2-dicarboxylic acid; (cis+trans)-1,4-cyclohexandicarboxylic acid; pyrazine-2,5-dicarboxylic acid; piperidine-2,6-dicarboxylic acid; piperidine-3,3-dicarboxylic acid; pyrroline-N-oxide-5,5-dicarboxylic acid; γ-pyrone-2,6-dicarboxylic acid and piperazine-2,6-dicarboxylic acid.

With respect to the biradical B, it is believed that this can be an aliphatic biradical of the formula

$$-(CR^3R^4)_n-$$

where R^3, R^4 and n are as defined above for A.

Alternatively, B could be derived from an aliphatic or aromatic amino alcohol, e.g., as illustrated in Figure 3, wherein X is selected from the group consisting of >NR⁶, >NH, -O-, -S-, -Se-, -Te-, -CR^1R^2-, >C=O, >C=S, and Y^1, Y^2, R^1, and R^2 each independently designates substituents as defined as optional substituent for aryl and heteroaryl (see above); or Y^1 together with Y^2 may form a biradical which together with the atoms located between these substituents, form(s) a 4-, 5-, 6-, 7- or 8-membered ring which may be an optionally substituted non-aromatic carbocyclic or heteroaromatic ring or an optionally substituted aromatic or heteroaromatic rings; and each Z^1 and Z^2 independently designates =N-, =N⁺R⁵-;

Preferred examples of the biradical B are, e.g., biradicals of the following non-aromatic carbocyclic compounds: cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclopentadiene, cyclohexane, cycloheptane and cyclooctane; the following aromatic or non-aromatic heterocyclic compounds: epoxides, aziridines, thioepoxides, oxazetane, diazetane, thiazetane, oxazolane, imidazolidine, thiazolane, oxazilane, hexahydropyridazine, thiazilane, oxazepane, diazepane, thiazepane, oxazocane, diazocane, thiazocane, tetrahydrofuran, dihydrofuran, pyrrolidine, tetrahydrothiophen, tetrahydropyran, piperidine, tetrahydrothiopyran, oxepane, azepane, thiepane, oxocane, azocane, thiocane, cyclopropane, oxirane, aziridine, cyclopropene, azirine, cyclobutane, oxetane, azetidine, thietane, 2-azetidinone, 1,3-lactone, pyrrolidine, pyrroline, pyrrole, pyrrolidione, pyrrolidone, oxirane, dioxirane, morpholine, piperidine, 1,5-lactone, 1,5-lactam, cyclohexene, cyclohexadiene, piperidione, tropane, 1,6-lactone (tropolone), 1,6-lactam, azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine

As appears from the above, each of L^1 and L^2 independently designates -NR⁵- or -O-, wherein each R⁵ independently is selected from hydrogen, optionally substituted C_{1-20}-alkyl, optionally substituted C_{2-20}-alkenyl, optionally substituted C_{4-20}-alkadienyl, optionally substituted C_{6-20}-alkatrienyl, optionally substituted aryl, and optionally substituted heteroaryl, or R⁵ designates an additional bond to B (whereby B becomes a triradical). Preferably R⁵ designates hydrogen, C_{1-4}-alkyl or an additional bond to B. In particular, one of L^1 and L^2 is -O- and the other is -NR⁵-, where R⁵ designates hydrogen, C_{1-4}-alkyl or an additional bond to B.

Thus, interesting and highly relevant starting materials for the preparation of the compounds I are 1-amino-ω-hydroxy-(optionally substituted)-C_{1-6}-alkylene, where C_{1-6}-alkylene is the biradical of the radicals defined for C_{1-6}-alkyl and optional substituents are as defined for "alkyl".

When the aminoalcohol is selected from the group of non-aromatic carbocyclic compounds or heterocyclic compounds the hydroxy- and amino-function can be positioned 1,2-, 1,3-, 1,4- or 1,5-, where applicable, to each other as well as the stereochemical environment of the amino and alcohol groups can be positioned either in a *cis*-configuration where the two substituents are on the same side of the ring or could be positioned *trans*-configuration where the two substituents are on the different side of the ring system. Likewise, different enantiomers (mirror images) and diastereoisomers can exist as an inherent result of the chirality in such substituted non-aromatic carbocyclic compounds or heterocyclic compounds. Thus, especially preferred examples are aminoalcohols derived from non-aromatic carbocyclic and heterocyclic compounds where the hydroxy and amino function are positioned 1,2 or 1,3 relative to each other, especially 1,2 to each other.

Specific examples of aminoalcohols derived from non-aromatic carbocyclic compounds are 2-aminoethanol, 1-amino-2-propanol, 3-amino-1-propanol, 2-amino-1-propanol, 2-amino-2-methyl-1-propanol, 1-amino-2-methyl-2-propanol, 3-amino-2-methyl-1-propanol, 2-amino-1-butanol, 1-amino-2-butanol, 3-amino-3-butanol, 3-amino-1-butanol, 4-amino-2-butanol, *cis*-2-amino-1-cyclobutanol, *trans*-2-amino-1-cyclobutanol, 5-amino-1-pentanol, 2-amino-1-pentanol, 3-amino-2-pentanol, 2-amino-3-pentanol, 1-amino-2-pentanol, *cis*-2-amino-1-cyclopentanol, *trans*-2-amino-1-cyclopentanol, 6-amino-1-hexanol, *trans*-4-amino-1-cyclohexanol, *cis*-4-amino-1-cyclohexanol, *trans*-2-amino-1-cyclohexanol, *cis*-2-amino-1-cyclohexanol, *cis*-2-amino-1-cyclohexanol, *cis*-2-amino-4-methyl-1-cyclohexanol, *cis*-2-amino-5-methyl-1-cyclohexanol, *trans*-2-amino-1-cycloheptanol, *cis*-2-amino-1-cycloheptanol, *trans*-2-amino-1-cyclooctanol, *cis*-2-amino-1-cyclooctanol.

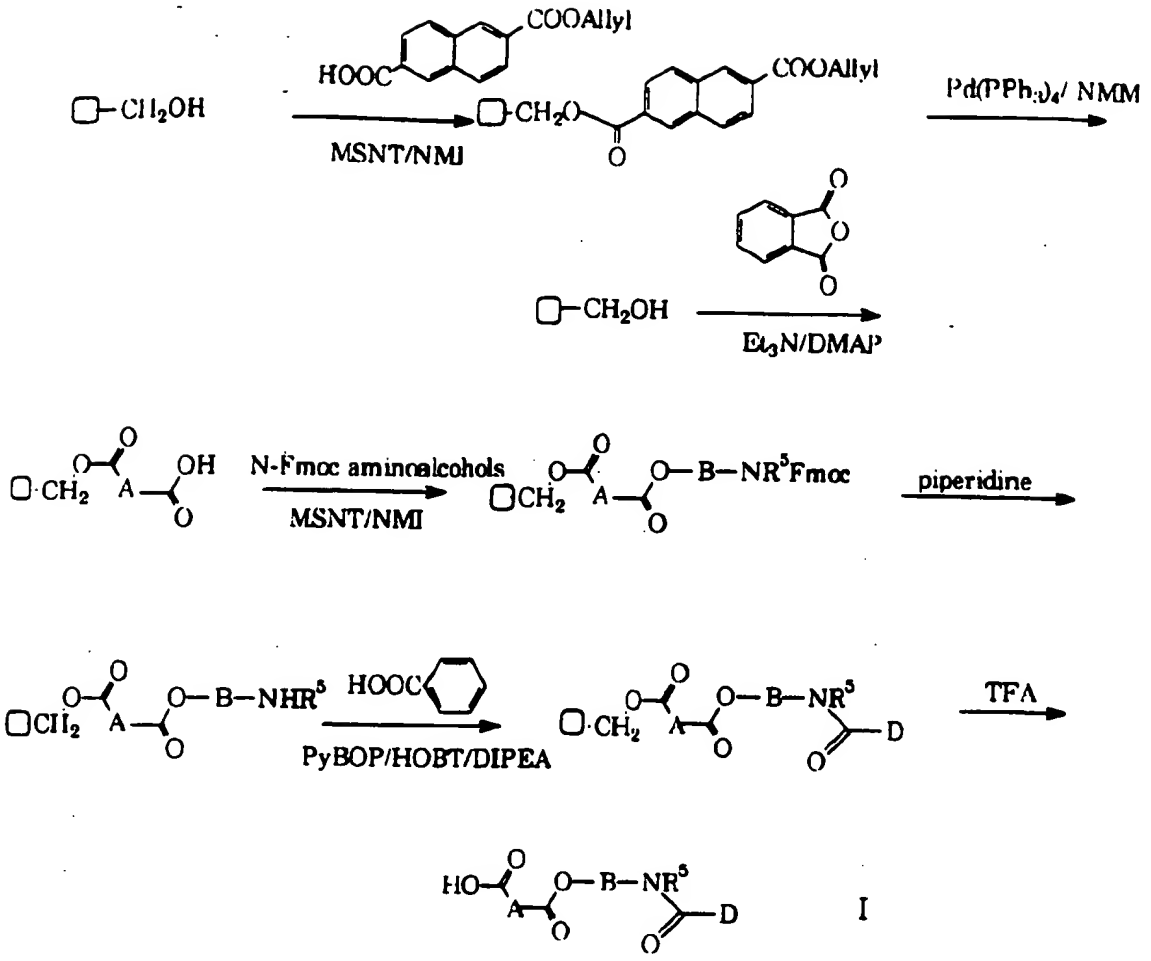
Specific examples of aminoalcohols derived from heterocyclic compounds are *cis*-4-amino-3-hydroxy-pyrolidine, *trans*-4-amino-3- hydroxy-pyrrolidine, *cis*-4-amino-3-hydroxy-tetrahydrofuran, *trans*-4-amino-3-hydroxy- tetrahydrofuran, *cis*-4-amino-3-hydroxy-tetrahydrothiophen, *trans*-4-amino-3-hydroxy-tetrahydrothiophen, *cis*-3-amino-4-hydroxy-piperidine, *trans*-3-amino-4-hydroxy-piperidine, *cis*-4-amino-3-hydroxy-piperidine, *trans*-4-amino-3-hydroxy-piperidine, *cis*-5-amino-3-hydroxy-piperidine, *trans*-5-amino-3-hydroxy-piperidine, *cis*-4-amino-3-hydroxy-tetrahydro-2H-pyrane, *trans*-4-amino-3-hydroxy-tetrahydro-2H-pyrane, *cis*-4-amino-3-hydroxy-tetrahydro-2H-thiopyrane, *trans*-4-amino-3-hydroxy-tetrahydro-2H-thiopyrane, *cis*-5-amino-4-hydroxy-2-piperidone, *trans*-5-amino-4-hydroxy-2-piperidone, *trans*-3-amino-4-hydroxy-azepane, *cis*-3-amino-4-hydroxy-azepane, *trans*-4-amino-3-hydroxy-azepane, *cis*-4-amin -3-hydroxy-azepane, *trans*-5-amino-4-hydroxy-azepane, *cis*-5-amino-4-hydroxy-azepane, *trans*-3-amino-4-

hydroxy-oxepane. *cis*-3-amino-4-hydroxy-oxepane. *trans*-3-amino-4-hydroxy-azocane. *cis*-3-amino-4-hydroxy-azocane.

The fragment D-C(=O) in the formula I is obviously derived from an aromatic carboxylic acid or a derivative thereof. Thus, it is believed that a huge number of readily (and also commercially) available starting materials for the preparation of the compound I can be utilised. Furthermore, the chemistry of aromatic compound is quite developed, so the group of accessible compound may be further supplemented.

Preparation of the compounds of the general formula I

The synthesis of the compounds I is exemplified in the following Scheme 2. With reference to the general formula I, the biradical A is shown in the schemes as 2,6-naphthylene and 1,2-phenylene, respectively. The biradical B may be an aliphatic or non-aromatic carbocyclic or heterocyclic group or an aromatic or heteroaromatic group. The end group K is OH, L^1 is -O-, L^2 is $-NR^5-$, and D is phenyl. Furthermore, the solid phase material, symbolised with a box, is a Wang resin.



Scheme 2

The example illustrated in Scheme 2 represents two possible embodiments of the method according to the invention. Thus, in each of the steps (A)-(D), variations are possible. In the following general guidelines for each of the steps of the method according to invention are given:

Step (A): an optionally functional group protected moiety -C(=O)-*A*-C(=O)-M¹ immobilised to a solid support material, wherein -C(=O)-M¹ designates a carboxy group or a derivative thereof, is provided.

As illustrated in Scheme 2, various possibilities for the immobilisation are comprised within the scope of the present invention. Normally, it is preferred to use the diacid in monoester form, in that use of the dicarboxylic acid may lead to side product formation due to the lack of mono-selectivity in the reaction between the activated solid phase material and the diacid. Thus, it is believed, and can also be demonstrated, that used of the dicarboxylic acid in the free acid form will lead to a lower yield, such a lower yield may, however, compensate for the resources used when preparing, e.g., the monoester.

Another example is the case where an internal anhydride of a dicarboxylic acid is used. In the cases where the dicarboxylic acid is mono-protected, the protecting group is preferably removed in order to provide the carboxy functionality in a form, C(=O)-M^1, ready for coupling in step (B). Thus, the group M^1 preferably designates OH or O^-. The conditions for coupling the dicarboxylic acid to the solid phase material is closely connected to the choice of solid phase material and linker, and will be described further below.

Step (B): an optionally functional group protected difunctional entity L'^1-B-L'^2 is coupled to the -C(=O)-M^1 end of the immobilised moiety -C(=O)-A-C(=O)-M^1 for the formation of an optionally functional group protected immobilised fragment -C(=O)-A-C(=O)-L^1-B-L'^2.

First of all, the group -C(=O)-M^1 should be present in a form susceptible to reaction with the entity L'^1-B-L'^2, thus, as described above, -C(=O)-M^1 is preferably a carboxy group or a carboxylate group, or, alternatively, in reactive form, e.g. in active ester form. Preferably M^1 is OH or O^-. It is clear that the group L'^1 of the entity L'^1-B-L'^2 should end up as L^1 in the compound I. Thus, L'^1 is, in the case where L^1 designate -O-, a hydroxyl group or a derivative thereof, preferably a hydroxyl group. In the case where L^1 designate -NR^5-, the group L'^1 is preferably the free amino group or a derivative thereof which, under the reaction conditions, will liberate a free amino group. Preferably L'^1 is the free amino group, either a primary amine, i.e. R^5 is hydrogen, or a secondary amine, i.e. R^5 is, e.g., an C_{1-4}-alkyl group or designates an additional bond to B.

As the group L'^2 should remain unaffected by the reaction conditions, it preferably designates a protected hydroxy group or a protected primary or secondary amine. Examples of groups L'^2 are -O-P (where L^2 is -O-), where P designate a hydroxy protection groups selected from dimethoxytrityl (DMT), monomethoxytrityl (MMT), trityl, 9-(9-phenyl)xanthenyl (pixyl), tetraahydropyranyl (thp), methoxytetrahydropyranyl (mthp), trimethylsilyl (TMS), triisopropylsilyl (TIPS), *tert*-butyldimethylsilyl (TBDMS), triethylsilyl, phenyldimethylsilyl, benzyloxycarbonyl, substituted benzyloxycarbonyl ethers such as 2-bromo benzyloxycarbonyl, *tert*-butylethers, methyl ethers, acetyl, halogen substituted acetyls such as chloroacetyl and fluoroacetyl, isobuteryl, pivaloyl, benzoyl, substituted benzoyls, methoxymethyl (MOM), benzyl ethers, and substituted benzyl ethers such as 2,6-dichlorobenzyl (2,6-Cl_2Bzl), and -NR^5-P (where L^1 is -NR^5-), where P designates an amino protection groups selected from Fmoc (fluorenylmethoxycarbonyl), BOC (*tert*-butyloxycarbonyl), trifluoroacetyl, allyloxycarbonyl (alloc, AOC), benzyloxycarbonyl (Z, Cbz), substitued benzyloxycarbonyls such as 2-chloro benzyloxycarbonyl ((2-ClZ), DDE (Bloomberg, G.B., *et al.*, *Tetrahedron Lett.* 1993, 34, 4709-4712), monomethoxytrityl (MMT), dimethoxytrityl (DMT), and 9-(9-phenyl)xanthenyl (pixyl).

The coupling reaction in step (B) will often include a coupling reagent, e.g. a reagent which converts the group -C(=O)-M¹ into an active derivative, e.g. an active ester or an acid halide. A number of highly effective coupling reagents and activated forms of carboxylic acids are know by the person skilled in the art of amide bond formation (peptide chemistry). Illustrative examples include the use of PyBrOP (Coste, J.; Frerot, E.; Jouin, P. and Castro, B. *Tetrahedron Lett.* **1991**, *32*, 1967-1970), amino acid fluorides (Carpino, L. A.; Sadat-Aalaee, D.; Chao, H. G. and DeSelms, R. H. *J. Am. Chem. Soc.*) and HATU (Carpino, L. A. *J. Am. Chem. Soc.*, **1993**, *115*, 4397-4398; Angell, Y. M.; Garcia-Echeverria, C. and Rich, D. H. *Tetrahedron Lett.* **1994**, *35*, 5981-5984, and Angell, Y. M.; Thomas, T. L.; Flenkte, G. R. and Rich, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 7279-7280), PyBOP (Frérot, E., et al., Tetrahedron, 1991, 47(2), pp 259-270), and CF_3-NO_2-PyBOP (Wijkmans, J.C.H.M., et al, Tetrahedron Lett. 1995, 36(26), pp 4643-4646). A coupling reagent will be equally applicable for the formation of an amide bond as for the formation of an ester bond.

Step (C): an optionally functional group protected entity D-C(=O)-M², wherein C(=O)-M² designates a carboxy group or a derivative thereof, is coupled to the L'² end of the immobilised fragment -C(=O)-A-C(=O)-L¹-B-L'² for the formation of an optionally functional group protected immobilised compound -C(=O)-A-C(=O)-L¹-B-L²-C(=O)-D, the step optionally including deprotection of any protection group involved in L'².

As described under step (B), the group L'² typically includes a protecting group, thus, in that case, such a group should preferably be removed before coupling of the entity D-C(=O)-M² to the immobilised fragment. With respect to the group -C(=O)-M², it may be a carboxy group or derivative thereof. In one variant the group -C(=O)-M² is a reactive derivative of a carboxylic acid, e.g. an active ester or the acid halide, e.g. the acid chloride or fluoride. In another variant, the group -C(=O)-M² is the free acid or the carboxylate thereof. In the latter case, the reaction typically involves the use of a coupling agent. Thus, M² may designate OH, O^-, halogen such as fluoro or chloro, or the remainder of an active ester.

Step (D): the compound K-C(=O)-A-C(=O)-L¹-B-L²-C(=O)-D is cleaved from the solid support material, the step optionally including deprotection of one or more functional group(s) attached to A, B, and/or D.

The conditions for cleaving the compound from the solid phase material is described below in connection with the examples of solid phase materials. The cleavage step may, where applicable include deprotection of one or more protected functional groups. It should be understood that deprotection may be performed before cleavage or after cleavage of the compound from the solid

phase material. Furthermore, in an interesting instance, deprotection is performed simultaneously to cleavage of the compound from the solid phase material. The latter possibility applies when a Wang resin is used. In this instance trifluoroacetic acid (TFA) is used for cleavage of the compound and deprotection of any Boc amino protecting groups.

In the present context the term "optionally functional group protected" and similar terms are intended to mean that in the case where any of the groups in question, e.g. any or all of A, B, and D, comprises a chemical functionality (or several chemical functionalities) which is/are susceptible to reaction, alteration or degradation under the reaction conditions in question or due to the lack of regioselectivity of the reagents used, such chemical functionalities may be protected. Protection of the starting materials may be performed, or protection may be performed prior to the potentially harmful reaction in a separate reaction step or protection may be included in the reaction step. Protection of chemical functionalities may also become relevant in the cases where the unprotected variant of the compound in question is difficult or virtually impossible to purify. In such cases a protection-purification-deprotection scheme may be applied. Protecting groups were used according to state-in-the-art procedures such as those described by Greene, T. W. and Wuts, P. G. M. (Protecting Groups in Organic Synthesis). Preferred protecting groups are the protecting groups frequently used in solid-phase syntheses, peptide synthesis (see *e.g.* Steward, J. M. & Young, J. D., Solid Phase Peptide Synthesis, Pierce Chemical Company (1984) or Robert C. Sheppard E. Atherton, Solid-Phase Peptide Synthesis, IRL Press, 1989), oligonucleotide synthesis (see *e.g.* M.J. Gait, Oligonucleotide Synthesis, IRL Press, 1984), oligosaccharide synthesis, organic synthesis and during synthesis of natural products. Protection groups are especially relevant for the amino groups, hydroxy and mercapto groups, and carboxy groups in that they may directly interfere with the reactions performed in the steps (B) and (C). Thus, protection groups, among numerous are well know to the person skilled in the art, may not just be desirable but also necessary in order to suppress side product formation.

Possible protection groups comprise, but is not limited to, the amino protection groups such as Fmoc (fluorenylmethoxycarbonyl), BOC (*tert*-butyloxycarbonyl), trifluoroacetyl, allyloxycarbonyl (alloc, AOC), benzyloxycarbonyl (Z, Cbz) or substitued benzyloxycarbonyls such as 2-chloro benzyloxycarbonyl ((2-ClZ), DDE (Bloomberg, G.B., *et al.*, *Tetrahedron Lett.* 1993. 34, 4709-4712), monomethoxytrityl (MMT), dimethoxytrityl (DMT), and 9-(9-phenyl)xanthenyl (pixyl); hydroxy protection groups such as dimethoxytrityl (DMT), monomethoxytrityl (MMT), trityl, 9-(9-phenyl)xanthenyl (pixyl), tetraahydropyranyl (thp), methoxytetrahydropyranyl (mthp), trimethylsilyl (TMS), triisopropylsilyl (TIPS), *tert*-butyldimethylsilyl (TBDMS), triethylsilyl, phenyldimethylsilyl, benzyloxycarbonyl or substituted benzyloxycarbonyl ethers such as 2-bromo benzyloxycarbonyl, *tert*-butylethers, methyl ethers, acetyl or halogen substituted acetyls such as chloroacetyl or fluoroacetyl, isobutyryl, pivaloyl, benzoyl and substituted benzoyls, methoxymethyl (MOM), benzyl ethers or substituted benzyl ethers such as 2,6-dichlorobenzyl (2,6-

Cl_2Bzl); carboxy protection groups such as allyl esters, methyl esters, ethyl esters, 2-cyanoethyl-esters, trimethylsilylethylesters, benzyl esters (Obzl), 2-adamantyl esters (O-2-Ada), cyclohexyl esters (Oc-hex), 1,3-oxazolines, oxazoler, 1,3-oxazolidines, amides or hydrazides, or in the form of an activated ester such as an N-hydroxysuccinimide or an symmetric or asymmetric anhydride; and mercapto protecting groups such as trityl (Trt), acetamidomethyl (acm), trimethylacetamido-methyl (Tacm), 2,4,6-trimethoxybenzyl (Tmob), *tert*-butylsulfenyl (S*t*Bu), 9-fluorenylmethyl (Fm), 3-nitro-2-pyridinesulfenyl (Npys), and 4-methylbenzyl (Meb).

Deprotection of any "optionally protected functional groups" is performed by methods known by the person skilled in the art, e.g. as described in Greene, T. W. and Wuts, P. G. M. (Protecting Groups in Organic Synthesis).

The compounds of the invention may be prepared by any well known methods or coupling reactions for the preparation of amide and ester bonds. Such coupling reactions for establishing amide bonds, as well as ester bonds, between an compound fragment immobilised to a solid phase material and a second chemical species are known for the person skilled in the art of solid phase synthesis. An example is the well-established Merrifield solid phase synthesis methodology (e.g. Barany, G., and Merrifield, R.B. in *The Peptides, Vol. 2*, Academic Press, New York, 1979, pp. 1-284).

In the present context the term "solid phase material" is intended to comprise solid phase materials know in the art. Especially suitable solid phase materials (polymers) are based on polystyrene cross-linked with 0.2-2% divinylbenzene and functionalised as described in the literature to yield resin of the so-called "Wang-type" (Wang, S. -S., *J. Am. Chem. Soc.*, 1973, 94, 1328-1333) a *para*-alkoxybenzyl alcohol resin which yields the free acid upon treatment and cleavage with trifluoroacetic acid/dichloromethane (1:1, v/v) for 30 minutes at room temperature or a resin of the so-called "Rink-type" (Rink, H. *Tetrahedron Lett.*, 1987, 28, 3787-3790)) a trialkoxy-diphenyl-methylester resin which yields the acid amide upon treatment and cleavage with trifluoroacetic acid/dichloromethane (3:7, v/v) for 60 minutes at room temperature. Likewise, the resins can be based on polystyrene cross-linked with 0.2-2% divinylbenzene and grafted with polyethyleneglycol (PEG) to yield the so-called "TentaGel resin" which have better and more uniform swelling characteristics in polar solvents that the parent polystyrene resins (Bayer, E. *Angew. Chem. Int. Ed. Engl.*, 1991, 30, 113-129). Resins of similar characteristics given from PEG-modified are commercial available with many different functionalities and are sold under trade names such as ArgoGel, PEGA resin or PEG-PS from various different vendors (e.g. Argonaut Inc., Peptide Laboratories, NovaBiochem, etc.).

In a further embodiment of the methods of present invention, the compound I may after cleavage from the solid phase material undergo a further reaction step (E) for the formation of another

compound of the general formula I. This reacti n step may be especially relevant when modification of the group K-C(=O)- is desired due to the fact that the variability of this group is governed by the applicable method for cleavage of the compound from the resin.

Preparation of monoesters of dicarboxylic acids

As the first step in the preparation of the compounds I involves the moiety -C(=O)-A-(=O)-, it is evident that a diacid HOOC-A-COOH, e.g. in the free acid, monoester, or internal anhydride form, may be used when providing the immobilised moiety -C(=O)-A-C(=O)-M¹

In order to be able to utilise a wide range of bifunctional aromatic and heteroaromatic molecules in the synthesis of compounds I, the accessibility to synthetic routes towards, e.g., aromatic dicarboxylic acid monoesters are advantageous. Three different syntheses have been described in Tong, G. and Nielsen, *J. Bioorg. Med. Chem.* **1996**, 4, 693-698.. The first method is based on the esterification, in particular the allylation, of the monocesium salt of a dicarboxylic acid, exemplified herein as esterification of naphthalene-2,6-dicarboxylic acid with allyl bromide (Example 3). The second one is based on the use of anion exchange resins to block off one of the carboxylic acid groups while the other undergoes esterification (Blankemeyer-Menge, B.; Nimtz, M. and Frank, R. *Tetrahedron Lett.* **1990**, *31*, 1701-1704). A third possible route it the selective deesterification of dicarboxylic acid diesters. A further possibility is using phase transfer chemistry (Friedrich-Bochnitschek S., *J. Org. Chem.* 54, **1989**, 751-756). Advantageous conditions for the production of the monoester with a minimum yield of the diester were an equimolar amount of Cs_2CO_3 added in small portions over an extended period such as 16 h, and 2 equivalents of allyl bromide. Obtainable yields of the purified monoester are at least 30%. An alternative method based on the adsorption of the naphthalene diacid onto an anion exchange resin followed by reaction with mesithylenesulphonylnitrotriazolide (MSNT), N-methylimidazole and allyl alcohol produces the desired monoester. The third method is based on the possibility of mono-deesterification of certain aromatic dimethyl esters. Synthesis of the mixed methyl-allyl-diester followed by selective demethylation (NaCN/HMPA(hexamethylphosphoramide)) yields the corresponding monoallyl ester.

Preparation of libraries of compounds of the general formula I

The preparation of compound libraries of balanol analogues follows the same principles as described above for the preparation of single analogues. In order to ensure that a suitable amount of each of the theoretically obtainable compound were formed in a suitable am unt, the split-mix synthesis method (Furka, A.; Sebestyèn, F.; Asgedom, M.; Dibò, G. *Int. J. Peptide*

Protein Res. 1991. 37. 487-493) was applied. Other method may also be applicable within the context of the present invention.

Thus, the present invention further provides a method for the preparation of a multi-dimensional array, {A}-{B}-{D}, i.e. a combinatorial library, of compounds consisting of at least four compounds each having the general formula I

$$K\text{-}C(=O)\text{-}A\text{-}C(=O)\text{-}L^1\text{-}B\text{-}L^2\text{-}C(=O)\text{-}D \qquad I$$

as defined above. Such an array is constructed by combining an array {A} consisting of m compounds corresponding to the biradical -C(=O)-A-C(=O)- with an array {B} consisting of n compound corresponding to the biradical -L^1-B-L^2- and an array {C} consisting of o compound corresponding to the radical -C(=O)-D. The total number of compound is depending on the number of fragments, i.e. m, n, and o. These numbers, m, n, and o, are all positive integers, and in order for the multi-dimentional array to comprise at least four compound the product m·n·o must be at least 4. Although the combination where one of m, n, and o is four and the other two numbers each are one is possible within the method of the present invention, it is preferred that at least two of the numbers, preferably all three, are at least two, so that the highest degree of diversity of the combinatorial library is obtained. Thus, it also is preferred that the combinatorial library comprises in the range of 6-200 different compound, more preferably 6-100 different compounds, and in particular 8-64 different compounds.

As mentioned above, the preparation of a multi-dimensional array/library of compound follows the same principles as for the preparation of single compounds, and, thus, the synthetic scheme comprises the following steps (described for the case where the split-mix synthesis is used):

Step (A): an array {A} of m optionally functional group protected moieties -C(=O)-A-C(=O)-M^1 immobilised to a solid support material, wherein -C(=O)-M^1 designates a carboxy group or a derivative thereof, is provided. Following the split-mix synthesis, each of the types of immobilised moieties are synthesised individually, thus, each solid phase particle or entity, comprises only one type of moiety. After this step the solid phase material is pooled and split into n (see below) portions ready for the step (B). It should be understood that larger amounts of the immobilised moieties may be prepared leaving material for later experiments..

Step (B): an array {B} of n optionally functional group protected difunctional entities L'^1-B-L'^2 is coupled to the -C(=O)-M^1 end of the immobilised moieties -C(=O)-A-C(=O)-M^1 for the formation of an array {A}-{B} of m·n optionally functional group protected immobilised fragments -C(=O)-A-C(=O)-L^1-B-L'^2. Also in this step to coupling is preferably performed in n different batches where the reacted material is pooled and split for the next coupling step, i.e. step (C).

Step (C): an array {D} of o optionally functional group protected entities D-C(=O)-M^2, wherein -C(=O)-M^2 designates a carboxy group or a derivative thereof, is coupled to the L'^2 end of the immobilised fragments -C(=O)-A-C(=O)-L^1-B-L'^2 for the formation of an array {A}-{B}-{D} of m•n•o optionally functional group protected immobilised compounds -C(=O)-A-C(=O)-L^1-B-L^2-C(=O)-D, the step optionally including deprotection of any protection group involved in L'^2. Also in this step the coupling is preferably performed in o different batches. The reacted material need not necessarily to be pooled before cleavage in step (D).

Step (D): cleaving the array {A}-{B}-{D} of compounds K-C(=O)-A-C(=O)-L^1-B-L^2-C(=O)-D from the solid support material, the step optionally including deprotection of one or more functional group(s) attached to individual As, Bs, and/or Ds. It should be understood that the o different batches from step (C) may be cleaved individually or the batches may be pooled before cleavage. Pooling before cleavage may be advantageous seen from an economical and handling point of view. However, in the case where an analysis of the prepared library is to be performed, it is (of course) advantageous to operate with a relatively low number of compounds. Thus, the array of m•n•o compound may actually be present in o batches each containing m•n compound. These compound may then be pooled, e.g. before the actual screening is conducted. Alternatively, each of the batches may be screened individually. In a third and most interesting alternative, the library consisting of the combined batches (or a number of these) containing (up to) m•n•o compound is screened, and in the case where biological activity is identified, each of the o batches are screened individually thereby pointing back to one specific moiety D as biologically interesting. The principles of screening are discussed in the following.

Method of screening

Screening of combinatorial libraries may be performed in any of the ways generally used by scientists and technicians skilled in the art. These include but is not limited to screening of individual compounds, by deconvolution of libraries containing mixtures, by positional scanning of libraries of mixtures or by screening sub-libraries in an index library mode. Therefore, library formats could be as single compounds i.e. one vial would be containing one single compound, small mixtures of isomeric compounds where stereoisomer would be included in the form of enantiomers, diastereomers, geometrical or positional isomers, as mixtures of typically 10-100 compounds per vial to allow fast deconvolution down to the active substance, or as large mixtures of more than 100 compounds per vial to allow for rapid screening of vast combinatorial libraries. Screening are performed in assay formats usual for the high throughput mode, typically using 96 well format, 384 well format or other microplate formats compatible with automation in the search of enzyme inhibitors, receptor agonist, partial agonists, as well as neutral antagonists and negative antagonists (inverse agonists).

By such screening methods it is envisaged that biological activity of the compound I prepared according to the present invention will be demonstrated. Thus, it is believed that biological activity within one of the following fields can be shown:

(a) Biological effects interesting in the treatment of mammals such as human beings: anesthetics, central nervous system depressants such as sedative-hypnotics, anticonvulsants, neuroleptics and anxiolytic agents, drugs to treat neuromuscular disorders such as antiperkinsonism agents or skeletal muscle relaxants, analgesics, central nervous system stimulants, local anesthetics, cholinergic agonists, acetylcholinesterase inhibitors or cholinergic antagonists, adrenergic drugs, cardiac agents such as cardiac glycoside analogs, antianginals, and antiarrhythmic drugs, anticoagulants, coagulants, and plasma extenders, diuretics, antiallergic and antiulcer drugs, antilipidemic drugs, nonsteroidal anti-inflammatory drugs, drugs affecting sugar metabolism, antimycobacterial agents, antibiotics or antimicrobial agents, antifungal agents, antiseptics or disinfectants, as hormone antagonists, antineoplastic agents for cancer chemotherapy or photochemotherapy, antiviral agents or as a potential drugs against HIV-infections and AIDS.

(b) Biological effects interesting in the field of crop protection: compounds affecting sugar metabolism, antibiotics or antimicrobial agents, antifungal agents, such as pesticides, disinfectants, and hormone antagonists.

Thus, a further aspect of the invention is to provide novel compounds for the use as a medicament, and to provide the use of novel compounds for the manufacture of a medicament for one or more of the above mentioned. A still further aspect is to provide novel compound for the for the use in crop protection.

DESCRIPTION OF THE DRAWINGS

Figures 1 and 2 illustrate various examples of biradicals A. The meanings of the symbols are defined above.

Figure 3 illustrates various examples of biradicals B. The meanings of the symbols are defined above.

EXAMPLES

Example 1

Procedure for the synthesis of N-Fmoc-aminoalcohols

N-Fmoc-1-amino-2-propanol. Procedure as above starting from 1-amino-2-propanol. White solid (100%). Mp 120-123°C. ^{1}H NMR ($CDCl_3$) d 7.8 (d, 2H, J = 6.5 Hz), 7.6 (d, 2H, J = 6.5 Hz), 7.3 (m, 4H), 5.2 (m, 1H), 4.5 (d, 2H, J = 6.8), 4.2 (t, 1H, J = 6.8), 3.9 (m, 1H), 3.3-3.1 (m, 2H), 2.5 (m, 1H), 1.2 (d, 3H, J = 6.0)., ^{13}C NMR ($CDCl_3$) d 156.0 143.8 141.2 127.6 127.0 124.9 119.9 67.3 66.7 48.2 47.2 20.6.

N-Fmoc-2-amino-1-butanol. Procedure as above starting from 2-amino-1-butanol. White solid (96%). Mp 127-131°C. ^{1}H-NMR ($CDCl_3$) d 7.8 (d, 2H, J = 6.5 Hz), 7.6 (d, 2H, J = 6.5 Hz), 7.4 (m, 4H), 4.9 (m, 1H), 4.5 (d, 2H, J = 7 Hz), 4.2 (t, 1H, J = 7 Hz), 3.6 (m, 3H), 1.9 (m, 1H), 1.5 (m, 2H), 1.0 (t, 3H), ^{13}C-NMR ($CDCl_3$) d156.0 144.0 142.0 127.6 127.0 124.9 119.9 66.5 65.0 54.7 47.3 24.3 10.4.

N-Fmoc-3-amino-1-propanol. Procedure as above starting from 3-amino-1-propanol. White solid (95%). Mp 115-118°C. ^{1}H-NMR ($CDCl_3$) d 7.8 (d, 2H, J=6.5 Hz), 7.6 (d, 2H, J=6.5 Hz), 7.4 (m, 4H), 5.1 (m, 1H), 4.5 (d, 2H, J=7 Hz), 4.2 (t, 1H, J=7 Hz), 3.7 (m, 2H), 3.4 (q, 2H), 2.6 (m, 1H), 1.7 (p, 2H). ^{13}C-NMR ($CDCl_3$) d 142 136 128 127 125 120 67 60 48 38 33

***trans*-N-Fmoc-4-amino-cyclohexanol.** Procedure as above starting from *trans*-4-amino-cyclohexanol. White solid (37%). Mp 208-210°C. ^{1}H-NMR (DMSO-d_6) d 7.9 (d, 2H), 7.7 (d, 2H), 7.4 (m, 4H), 4.3 (m, 3H), 3.9 (m, 6H), 3.3 (s, 1H), 1.7 (m, 2H), 1.2 (m, 2H). ^{13}C-NMR (DMSO-d_6) d 155.3 143.9 140.7 127.6 127.0 125.2 120.0 68.1 65.1 49.2 46.8 34.0 30.5.

Example 2

Procedure for the synthesis of aromatic dicarboxylic acid

(a) Methylation of phenolic alcohol

2-Nitro-5-methyl-anisole. To a suspension of 4.6 g (30 mmol) 2-nitro-5-methyl-phenol and 20.7 g (150 mmol) dry K_2CO_3 in 150 ml acetone was added 42.6 g (300 mmol) MeI. The reacti n mixture was stirred at reflux 16 h, then cooled, filtered and concentrated *in vacuo*. The residue was redissolv d in EtOAc, filtered and concentrated *in vacuo* to afford light yellow solid 4.9 g

(98%). Mp 56-57°C. ^{1}H NMR ($CDCl_3$) d 7.8 (d, 1H, J = 8.4 Hz), 6.9 (s, 1H), 6.8 (d, 1H, J = 8.4 Hz), 4.0 (s, 3H), 2.4 (s, 3H). ^{13}C NMR ($CDCl_3$) d 153.1 145.9 125.8 120.8 113.9 108.5 56.2 21.8.

2-Methyl-3-nitro-anisole. Procedure as above starting from 2-methyl-3-nitro-phenol. Yellow solid (91%). Mp 51-52°C. ^{1}H NMR ($CDCl_3$) d 7.3 (d, 1H, J = 8.0 Hz), 7.2 (t, 1H, J = 8.0 Hz), 7.0 (d, 1H, J = 8.0 Hz), 3.9 (s, 3H), 2.3 (s, 3H). ^{13}C NMR ($CDCl_3$) d 158.2 150.8 132.1 126.5 115.4 113.6 55.9 11.2.

2-Nitro-3-methyl-anisole. Procedure as above starting from 2-nitro-3-methyl-phenol. Yellow solid (98%). Mp 46-48°C. ^{1}H NMR ($CDCl_3$) d 7.3 (t, 1H, J = 8.5 Hz), 6.9 (d, 1H, J = 8.5 Hz), 6.8 (d, 1H, J = 8.5Hz), 3.9 (s, 3H), 2.3 (s, 3H). ^{13}C NMR ($CDCl_3$) d 150.6 130.7 130.5 122.4 110.0 109.8 56.1 16.7.

(b) Hydrogenation of the nitro group

2-methoxy-4-methyl-aniline. To a solution of 4.9 g (29.3 mmol) 2-nitro-5-methyl-anisole in 100 ml EtOH and 5 ml conc. HCl under an N_2 atmosphere was added 250 mg 5% Pd on charcoal. The solution was hydrogenated at 200 psi and room temperature. After 16 h the reaction mixture was filtered through Celite and concentrated *in vacuo*. The residue was chromatographed in hexane-/EtOAc 1:1 to afford red oil 2.8 g (70%). ^{1}H NMR ($CDCl_3$) d 6.7 (m, 3H), 3.9 (s, 3H), 3.7 (s, 2H), 2.4 (s, 3H). ^{13}C NMR ($CDCl_3$) d 147.0 133.2 127.7 120.9 114.8 111.1 55.1 20.7.

2-methyl-3-methoxy-aniline. Procedure as above starting from 3-nitro-2-methyl-anisole. Red oil (60%). ^{1}H NMR ($CDCl_3$) d 7.1 (t, 1H, J = 8.0 Hz), 6.5 (dd, 2H, J = 8.0 Hz), 3.9 (s, 3H), 3.8 (s, 2H), 2.2 (s, 2H). ^{13}C NMR ($CDCl_3$) d 157.8 145.4 126.2 109.9 108.1 100.7 55.1 8.5.

(c) Diazotation of an amino group to a nitrile group (Sandmeier).

2-methyl-3-methoxy-benzonitrile. A solution of 2.5 g (18 mmol) 2-methyl-3-methoxy-aniline in 55 ml 2N HCl was cooled to -5°C in a ice/salt bath and stirred for 30 min. A solution of 1.37 g (19.8 mmol) $NaNO_2$ in 28 ml H_2O was added dropwise at -5°C. The reaction mixture was stirred 30 min. and neutralised carefully with approximately 3.7 g Na_2CO_3, then a solution of 1.8 g (19.8 mmol) CuCN and 1.9 g (39.6 mmol) NaCN in 28 ml H_2O was added in one portion. After 18 h the reaction mixture was extracted with 3*100 ml $CHCl_3$. The combined organic phases was extracted with H_2O, dried with Na_2SO_4 and concentrated *in vacuo* to afford dark red oil 2.0 g (75%). IR-data 2222 cm^{-1} (CN). ^{1}H NMR ($CDCl_3$) d 7.2 (q, 1H, J = 7.7 Hz), 7.15 (dd, 1H, J = 7.7 Hz, J = 1.5 Hz), 7.0 (dd, 1H, J = 7.7 Hz, J = 1.5 Hz), 3.9 (s, 3H), 2.4 (s, 3H). ^{13}C NMR ($CDCl_3$) d 157.5 130.8 127.1 123.7 117.9 113.9 113.5 55.4 14.1.

(d) Synthesis of benzophenone.

3,3'-dimethyl-benzophenone. To 3.6 g (110 mmol) Mg-turnings under 10 ml THF was added a Iodine Crystal and ¼ of 17.1 g (100 mmol) 3-bromotoluene. The mixture was heated to 40°C and after a while the Grignard reaction started. The rest (3/4) of the 3-bromotoluene in THF was added in such a rate to maintain reflux. After addition the reaction mixture was reflux for 1 h. cooled to room temperature and added dropwise to a solution of 7.3 g (63 mmol) 3-methyl-benzonitrile in 40 ml toluene at room temperature, then kept at 70°C for 16 h. The reaction mixture was cooled on an ice bath and 33 ml conc. HCl was added dropwise followed by 170 ml MeOH and refluxed 7 h. The reaction mixture was cooled, 100 ml H_2O was added and extracted with EtOAc. The combined organic phases was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was chromatographed (hexane/EtOAc 19:1) to afford colourless oil 10.5 g (80%). ^1H NMR ($CDCl_3$) d 7.6 (m, 2H), 7.3 (m, 2H), 2.4 (s, 3H). ^{13}C NMR ($CDCl_3$) d 196.7 137.8 137.5 132.8 130.1 127.7 127.0 21.0.

2,4'-dimethyl-benzophenone. Procedure as above starting from 2-bromotoluene and 4-methyl-benzonitrile. Colourless oil (77%). ^1H NMR ($CDCl_3$) d 7.7 (d, 2H, J = 8.2 Hz), 7.4-7.2 (m, 6H), 2.4 (s, 3H), 2.3 (s, 3H). ^{13}C NMR ($CDCl_3$) d 198.0 143.8 138.7 136.2 134.9 130.7 130.1 129.8 129.0 128.0 124.9.

2-methoxy-2',5-dimethyl-benzophenone. Procedure as above starting from 2-bromo-4-methyl-anisole and 2-methyl-benzonitrile.THF used instead of toluene. Colourless oil (36%). ^1H NMR ($CDCl_3$) d 7.4-7.1 (m, 6H), 6.8 (d, 1H, J = 8.0), 3.6 (s, 3H), 2.5 (s, 3H), 2.3 (s, 3H). ^{13}C NMR ($CDCl_3$) d 198.3 156.0 139.2 137.7 133.0 130.9 130.6 130.0 129.5 129.0 126.0 124.9 111.7 55.6 20.5 20.1.

2-methoxy-4',5-dimethyl-benzophenone. Procedure as above starting from 2-bromo-4-methyl-anisole and 4-methyl-benzonitrile. Chromatographed in (hexane/EtOAc 9:1). colourless oil (56%). ^1H NMR ($CDCl_3$) d 7.7 (m, 2H), 7.3-7.1 (m, 4H), 6.9 (d, 1H, J = 8.4 Hz), 3.7 (s, 3H), 2.4 (s, 3H), 2.3 (s, 3H). ^{13}C NMR ($CDCl_3$) d 196.8 155.0 143.6 135.1 131.9 129.9 129.6 128.8 111.3 108.7 55.6 21.6 20.2.

(e) Synthesis of benzophenone via benzhydrole.

4,4'-dim thyl-benzhydr le. To 3.6 g (150 mmol) Mg-turnings under 10 ml THF was added a Iodine Crystal and ¼ of 17.1 g (100 mmol) 4-bromotoluene. The mixture was heated to 40°C and after a while the Grignard reaction started. The rest (3/4) of the 4-bromotoluene in THF was

added in such a rate to maintain reflux. After addition the reaction mixture was reflux for 1 h, cooled to 0°C and the remaining Mg-turnings was removed. A solution of 12.3 g (103 mmol) 4-methyl-benzaldehyde in 20 ml THF at 0°C was dropwise added. After 2 h the reaction mixture was quenched with 200 ml ice, temperature allowed to rise to room temperature and 25% H_2SO_4 was added until solution was clear. The reaction mixture was extracted with DCM. The combined organic phases was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was recrystalised in heptane to afford white solid 10.6 g (50%). Mp 64-65°C. ^1H NMR ($CDCl_3$) d 7.2 (d, 4H, J = 8.1 Hz), 7.1 (d, 4H, J = 8.1 Hz), 5.8 (s, 1H), 2.3 (s, 6H). ^{13}C NMR ($CDCl_3$) d 141.1 137.1 129.1 126.4 77.5 21.1.

4,4'-dimethyl-benzophenone. To a suspension of 12.96 g (60 mmol) pyridinium chloro chromate in 60 ml DCM was added 6.36 g (30 mmol) 4,4'-dimethyl-benzhydrole. The mixture was stirred 24 h and 240 ml diethylether was added. The reaction mixture was filtered 3X through silica gel and concentrated *in vacuo* to afford white solid 3.7 g (59%). Mp 92-94°C. ^1H NMR ($CDCl_3$) d 7.7 (d, 4H, J = 7.9 Hz), 7.3 (d, 4H, J = 7.9 Hz), 2.4 (s, 6H). ^{13}C NMR ($CDCl_3$) d 196.2 142.8 135.1 130.1 128.8 21.5.

(f) Procedure for the Synthesis of methyl-methylphenyl-benzene

2-methyl-(4-methylphenyl)-benzene. To a solution of 5.2 g (24 mmol) 2-Iodotoluene in 12 ml diethylether under an atmosphere of N_2 at -78°C was dropwise added 32 ml 1.5 M (48 mmol) *tert*-BuLi in hexane. The reaction mixture was stirred 1 h at -78°C and 1 h at room temperature followed by concentration *in vacuo*. To the residue was added 16 ml THF at 0°C and the reaction mixture was dropwise added to a solution of 3.3 g (24 mmol) dry $ZnCl_2$ in 12 ml THF under an atmosphere of N_2 at 0°C. The reaction mixture was stirred 1 h at room temperature, then added to a solution of 3.4 g (20 mmol) 4-bromo-toluene. 0.23 g (0.2 mmol) $Pd(PPh_3)_4$ in 20 ml THF under an atmosphere of N_2 cooled in a water bath. The reaction mixture was stirred 16 h at 50°C, cooled and poured in a solution of 20 ml diethylether and 60 ml 4N HCl. The mixture was extracted with 2*40 ml ether. The combined organic phases was washed with $NaHCO_3$ (sat.), dried with $MgSO_4$ and concentrated *in vacuo* to afford colourless oil 2.0 g (47%). ^1H NMR ($CDCl_3$) d 7.2 (m, 8H), 2.3 (s, 3H), 2.2 (s, 3H).

(g) Aromatic Side Chain Oxidation of methyl-groups

Biphenyl-2,4'-dicarboxylic acid. To a solution of 5.2 g (33 mmol) $KMnO_4$ in 48 ml 50% pyridine (aq.) at 100°C was added 0.6 ml conc. NaOH and a solution of 2.0 g (11 mmol) 2-methyl-(4-methylphenyl)-benzene in 15 ml pyridine followed by 15 ml H_2O. The reaction mixture was stirred 1 h and 5.2 g (33 mmol) $KMnO_4$ was added. This procedure was continued to a total of 41.6 g (264 mmol) $KMnO_4$ was added. The hot reaction mixture was filtered and the filter cake

was washed with 4*30 ml H_2O and 10 ml pyridine. The filtrate was cooled in a ice bath and acidified to pH = 1 with conc. HCl. Brine was added and the reaction mixture was extracted with 4*150 ml EtOAc. The combined organic phases was concentrated *in vacuo* to afford white solid 0.9 g (33%). Mp 270°C. ^{1}H NMR (DMSO-d_6) d 10.9 (broad, 2H), 8.0 (d, 2H, J = 8.0 Hz), 7.8 (d, 1H, J = 8.0 Hz), 7.6 (t, 1H, J = 8.0 Hz), 7.5 (t, 1H, J = 8.0 Hz), 7.45 (d, 2H, J = 8.0 Hz), 7.4 (d, 1H, J = 8.0 Hz). ^{13}C NMR (DMSO-d_6) d 169.3 167.3 145.5 140.4 132.1 131.2 130.5 129.5 129.1 128.6 128.6 127.9.

Benzophenone-2,2'-dicarboxylic acid. Procedure as above starting from 2,2'-dimethyl-benzophenone. White solid (69%). Mp 208-210°C. ^{1}H NMR (DMSO-d_6) d 8.7 (broad, 2H), 7.8 (d, 2H, J = 6.6 Hz), 7.6 (m, 4H), 7.4 (d, 2H, J = 6.6 Hz). ^{13}C NMR (DMSO-d_6) d 168.6 138.6 132.8 131.1 130.8 129.3 128.9.

Benzophenone-3,3'-dicarboxylic acid. Procedure as above starting from 3,3'-dimethyl-benzophenone. White solid (56%). Mp 330°C (decomp.). ^{1}H NMR (DMSO-d_6) d 8.25 (s, 2H), 8.25 (m, 1H), 8.1-7.85 (m, 3H), 7.7 (m, 2H). ^{13}C NMR (DMSO-d_6) d 194.8 166.6 137.0 133.8 133.4 131.2 130.2 129.3.

Benzophenone-4,4'-dicarboxylic acid. Procedure as above starting from 4,4'-dimethyl-benzophenone. White solid (66%). Mp 355°C (decomp.). ^{1}H NMR (DMSO-d_6) d 8.1 (d, 4H, J = 8.0 Hz), 7.8 (d, 4H, J = 8.0 Hz). ^{13}C NMR (DMSO-d_6) d 195.0 166.6 140.0 134.3 129.8 129.5.

Benzophenone-2,4'-dicarboxylic acid. Procedure as above starting from 2,4'-dimethyl-benzophenone. White solid (72%). Mp 241-243°C.
^{1}H NMR (DMSO-d_6) d 8.0 (m, 3H), 7.7 (m, 4H), 7.5 (d, 1H, J = 7.6 Hz). ^{13}C NMR (DMSO-d_6) d 166.9 166.7 141.5 140.5 134.5 132.7 130.1 129.6 129.6 128.9 127.5 127.5.

2-Methoxy-benzophenone-2',5-dicarboxylic acid. Procedure as above starting from 2-methoxy-2,5'-dimethyl-benzophenone. White solid (64%). Mp 224-227°C. ^{1}H NMR (DMSO-d_6) d 8.2-8.0 (m, 2H), 7.9-7.8 (m, 1H), 7.7-7.5 (m, 2H), 7.3 (m, 1H), 7.2 (m, 1H), 3.6 (s, 3H). ^{13}C NMR (DMSO-d_6) d 195.0 167.5 166.5 143.5 135.2 132.9 132.4 130.8 129.6 129.1 126.3 122.6 112.9 56.1.

Example 3

Procedure for the synthesis of mono-allylated aromatic diacids

Benzophenone-2,2'-dicarboxylic acid mono allyl ester. To a solution of 1.08 g (4 mmol) Benzophenone-2,2'-dicarboxylic acid in 90 ml DMF was added 0.16 g (0.5 mmol) Cs_2CO_3. After 30

min. 0.34 ml (0.484 g, 4 mmol) allyl bromide. The reaction mixture was stirred 24 h and 0.16 g (0.5 mmol) Cs_2CO_3 was added. This procedure was continued until a total of 0.64 g (2 mmol) Cs_2CO_3 was added. After additional 24 h the reaction mixture was filtered and chromatographed ($CHCl_3$/AcOH 99:1) to afford 0.52 g (42%). Mp 205-207°C. Unreacted benzophenone-2,2'-dicarboxylic acid 0.312 g (29%) was isolated for reuse. ^1H NMR ($CDCl_3$) d 8.8 (broad, 1H), 8.0-7.3 (m, 8H), 6.0-5.7 (m, 1H), 5.3-5.1 (m, 2H), 4.7 (d, 2H, J = 7.0). ^{13}C NMR ($CDCl_3$) d 171.0 167.4 139.3 138.8 135.0 131.9 131.4 131.4 131.1 130.2 129.7 129.3 129.2 128.0 125.9 118.7 66.4.

Benzophenone-3,3'-dicarboxylic acid monoallyl ester. Procedure as above starting from benzophenone-3,3'-dicarboxylic acid. White solid (42%). Mp 140-143°C. ^1H NMR ($CDCl_3$) d 8.5 (m, 2H), 8.4-8.3 (m, 2H), 8.1-7.8 (m, 2H), 7.7-7.5 (m, 2H), 6.1-5.9 (m, 1H), 5.5-5.2 (m, 2H), 4.9 (d, 2H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) d 194.6 170.6 165.3 137.5 137.3 134.8 134.0 133.6 131.8 131.5 130.9 130.6 130.2 129.8 129.7 128.9 128.8 118.6 65.9.

Benzophenone-4,4'-dicarboxylic acid monoallyl ester. Procedure as above starting from benzophenone-4,4'-dicarboxylic acid. White solid (5%). Mp 263°C (decomp.). ^1H NMR (DMSO-d_6) d 11.7 (broad, 1H), 8.2 (m, 4H), 7.9 (m, 4H), 6.2-6.0 (m, 1H), 5.5-5.3 (m, 2H), 4.9 (d, 2H, J = 7.0 Hz).

Benzophenone-2,4'-dicarboxylic acid monoallyl ester. Procedure as above starting from benzophenone-2,4'-dicarboxylic acid. White solid (64%) of the 2 isomers in ratio 7:1 (2-allylester/4'-allylester). Chromatographed ($CHCl_3$/ MeOH/ triethylamine 8:1:1) to afford pure white solid of 2-allylester (39%) (Mp 125-127°C) and pure white solid of 4'-allylester (6%) (mp 119-120°C). 2-allylester: ^1H NMR ($CDCl_3$) d 10.8 (broad, 1H), 8.2-8.1 (m, 3H), 7.8 (d, 2H, J = 8.4 Hz), 7.4 (dd, 1H, J = 7.4 Hz, J = 1.6 Hz), 5.7 (m, 1H), 5.2 (m, 2H), 4.5 (d, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) d 196.2 170.8 165.3 141.0 140.9 132.8 132.6 131.2 131.0 130.8 130.2 129.9 129.0 128.9 127.6 125.2 118.7 66.1. 4'-allylester: ^1H NMR ($CDCl_3$) d 9.2 (broad, 1H), 8.1 (d, 3H, J = 8.2 Hz), 7.75 (d, 2H, J = 8.2 Hz), 7.7 (dt, 1H, J = 7.5 Hz, J = 1.2 Hz), 7.6 (dt, 1H, J = 7.5 Hz, J = 1.2 Hz), 7.4 (d, 1H, J = 7.5 Hz), 6.1-5.9 (m, 1H), 5.5-5.3 (m, 2H), 4.8 (d, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) d 196.3 170.1 165.3 141.9 140.2 133.7 133.3 131.7 130.8 129.8 129.8 129.6 129.0 127.8 127.5 127.4 118.5 65.9.

Biphenyl-2,2'-dicarboxylic acid monoallyl ester. Procedure as above starting from biphenyl-2,2'-dicarboxylic acid. Colourless oil (35%). Biphenyl-2,2'-dicarboxylic acid (40%) was isolated for reuse. ^1H NMR ($CDCl_3$) d 8.0 (m, 2H), 7.6-7.4 (m, 4H), 7.2 (d, 2H, J = 7.2 Hz), 5.7-5.6 (m, 1H), 5.2-5.0 (m, 2H), 4.5 (d, 2H, J = 5.9 Hz). ^{13}C NMR ($CDCl_3$) d 171.5 166.7 143.7 142.8 134.0 132.0 131.7 131.4 130.5 130.3 130.1 129.9 129.2 128.4 127.2 118.0 65.4.

Naphthoic-2,6-dicarb xylic acid m noallyl ester. Cs_2CO_3 (1.60g, 5.00 mmol) was added in two equal portions over 0.5 h to a solution of naphthoic-2.6-dicarboxylic acid (2.16g, 10.0 mmol) in anhydrous DMF (97 mL). Allyl bromide (17.3 mL, 200 mmol) was then added and the reaction mixture stirred vigorously for 24 h. The same amount of Cs_2CO_3 was then added in two equal portions over 8 h and the reaction allowed to proceed for a further 17 h. The precipitate was filtered and rinsed with DMF (3 x 20 mL). The combined filtrate was then concentrated *in vacuo* and extracted with hot 50% MeOH/acetone (2 x 100 mL). After evaporation of the solvent, residual starting material was removed by silica gel chromatography (acetone/hexane/HOAc, 50/48/2). The resulting fractions which contained a mixture of the monoester and the diester was concentrated, redissolved in 10 % MeOH/dichloromenthane, and treated with Amberlyst A-26 (hydroxide form) resin (24.0 g, 96 meq) for 17 h. The resin was then filtered and washed with fresh solvent (about 3 L) until no diester was detected in the effluent by TLC ($CHCl_3$/MeOH, HOAc, 94/4/2). The monoallyl ester was then eluted with MeOH/dichloromethane/acetic acid (10:80:10). After solvent removal, recrystallisation from acetone gave 3 as a fine colourless solid (0.77 g, 30 %); Mp 217-218°C. δ (250 MHz, DMSO-d_6): 4.88 (d, 2H, CH_2-CH=CH_2, J = 5.1 Hz), 5.30 (m, 1 H, CH_2-CH=CH_2), 5.45 (m, 1 H, CH_2-CH=CH_2), 6.10 (m, 1H, CH_2-CH=CH_2), 8.05 (m, 2H, H4 and H8), 8.25 (d, 2H, H1 and H3, J=8.4 Hz), 8.70 (dd, 2H, H5 and H7, J=15.5, 3.9 Hz). Elemental analysis ($C_{15}H_{12}O_4$): C: 69.77% (calcd. 70.3%): H: 4.51% (calcd. 4.72%). EIMS calculated for $C_{15}H_{12}O_4$ 256, found 256.

Example 4

Solid Phase Synthesis of Balanol Analogues

The balanol libraries was synthesised using *split-synthesis*-method. After each step the resins was mixed and swollen in a isopycnic mixture of 1,2-dichlorethane and DMF (2:1)and the resin was split for the next step in the synthesis. To analyse the contents attached to the resin, it was cleaved of the resin using a solution of 50% TFA in dichloromethane.

Two dicarboxylic acids were used in step (A) (m=2), four aminoalcohols were used in step (B) (n=4), and four aromatic carboxylic acid were used in step (C) (o=4). Thus, a library having 2·4·4=32 compounds was prepared.

(A) Coupling of aromatic acids to a Wang resin
(corresponding to step (A) in the general scheme)

Phthalic acid and naphthalene-2,6-dicarboxylic acid as the internal anhydride and th monoallyl esters, respectively, were coupled to a Wang resin using 2 different methods.

Coupling of phthalic acid to a Wang Resin. 1.6 g (0.87 meq/g) Wang resin (polystyrene cross-linked with 1% divinylbenzene from NovaBiochem) was swollen in 10 ml dry DMF and 2.83 g (1.6 mmol) phthalic-anhydride, 1.95 ml (1.425 g (14.1 mmol) Et_3N and 0.2346 g (1.92 mmol) DMAP was added. The reaction mixture was shaken for 4 days, then washed with 2*10 ml 30% MeOH in dichloromethane and 4*10 ml dichloromethane. The resin was dried and analysed on HPLC. Loading L = 0.66 meq/g.

Coupling of naphthalene-2,6-dicarboxylic acid monoallyl ester on Wang resin. 0.8 g (0.87 meq/g) Wang resin was swollen in 8 ml dry DMF and 0.321 g (1.25 mmol) naphthalene-2,6-dicarboxylic acid monoallyl ester, 0.412 g (1.39 mmol) MSNT and 0.443 ml (5.57 mmol) 1-methyl-imidazole (NMI) was added. The reaction mixture was shaken 4 days and washed with 2*10 ml 30% MeOH in dichloromethane and 4*10 ml dichloromethane. The resin was dried and analysed on HPLC. Loading L = 0.87 meq/g.

Deallylation of the immobilised naphthalene-2,6-dicarboxylic acid allyl ester. To a 5% HOAc and 2.5% NMM solution in 15 ml $CHCl_3$ was added 2.4 g (2.09 mmol) $Pd(PPh_3)_4$ under Argon. The mixture was shaken 10 min. and 0.8 g (0.87 meq/g, 0.696 mmol) mono-allylated resin was added under Argon. The reaction mixture was shaken 18 h and washed with 6*15 ml 0.5% DIPEA, 0.5 sodium-diethyl-dithio-carbamate in DMF for each 10 min. and 3*15 ml dichloromethane. The resin was dried and analysed on HPLC. Loading L = 0.83 meq/g.

Coupling of N-Fmoc-aminoalcohols on -COOH functionalised resin (corresponding to step (B))

Four different N-Fmoc-aminoalcohols were used.

***trans*-N-Fmoc-4-amino-1-cyclohexanol.** 0.4 g (0.87-0.66 meq/g) -COOH functionalised resin was swollen in 5 ml dry dichloromethane and a solution of 0.27 g (0.8 mmol) *trans*-N-Fmoc-4-amino-1-cyclohexanol in 5 ml dry dichloromethane was added. The reaction mixture was shaken 2 min. and 0.237 g (0.8 mmol) MSNT and 0.254 ml (3.2 mmol) NMI was added. After 4 days the reaction mixture was washed with 10 ml dichloromethane, 10 ml of 30% MeOH in DCM, 10 ml DMF and 2*10 ml DCM. The resin was dried and analysed on HPLC to identify the two products.

N-Fmoc-1-amino-2-propan l. Procedure as above using 0.238 g (0.8 mmol) N-Fmoc-1-amino-2-propanol. The two products was identified on HPLC.

N-Fmoc-2-amino-1-butanol. Procedure as above using 0.249 g (0.8 mmol) N-Fmoc-2-amino-1-butanol. The tw products was identified on HPLC.

N-Fmoc-3-amino-1-propanol. Procedure as above using 0.238 g (0.8 mmol) N-Fmoc-3-amino-1-propanol. The two products was identified on HPLC.

Coupling of benzoic acid derivatives on -NH_2 functionalised resin (corresponding to step (C))

Four different benzoic acids was used.

Diisopropylethylammonium salt of 4,4'-Dimethoxytrityl-oxymethyl-benzoic acid. 0.4 g (approx. 0.6 meq/g) -NH-Fmoc functionalised resin was washed with 2*10 ml 20% piperidine in DMF 2*40 min. and 3*10 ml DMF. The resin was swollen in 7 ml dry DMF and 0.584 g (1.0 mmol) diisopropylethylammonium salt of 4,4'-Dimethoxytrityl-oxymethyl-benzoic acid was added followed by addition of 0.520 g (1.0 mmol) PyBOP, 0.135 g (1.0 mmol) HOBT and 0.33 ml (2.0 mmol) DIPEA. After 4 days the resin was washed with 2*10 ml DMF, 2*10 ml 30% MeOH in DCM and 2*10 ml DCM for each 10 min.

4-nitro-benzoic acid. 0.4 g (approx. 0.6 meq/g) -NH-Fmoc functionalised resin was washed with 2*10 ml 20% piperidine in DMF 2*40 min. and 3*10 ml DMF. The resin was swollen in 7 ml dry DMF and 0.167 g (1.0 mmol) 4-nitrobenzoic acid was added followed by addition of 0.520 g (1.0 mmol) PyBOP, 0.135 g (1.0 mmol) HOBT and 0.33 ml (2.0 mmol) DIPEA. After 4 days the resin was washed with 2*10 ml DMF, 2*10 ml 30% MeOH in DCM and 2*10 ml DCM for each 10 min.

4-methoxy-benzoic acid. Procedure as above using 0.152 g (1.0 mmol) 4-methoxy-benzoic acid.

3-fluoro-benzoic acid. Procedure as above using 0.140 g (1.0 mmol) 3-fluoro-benzoic acid.

Cleavage of the combinatorial library from the Wang resin (corresponding to step (D))

In order to implement this synthesis on solid-phase, the outcome and optimisation of the key coupling reactions were followed by a *cleave-&-analyse* technique. Following this *cleave-&-analyse* technique, approximately 5 mg resin was weighted on an analytical balance and cleaved by trifluoroacetic acid (TFA)/dichloromethane (DCM) (1:1, v/v), evaporated (Speed-Vac™), redissolved and quantified by reverse-phase HPLC pre-calibrated using minimum three

standard concentrations. The products were cleaved by TFA/DCM (1:1, v/v) when a Wang-type resin was applied for the synthesis of the combinatorial library and analysed using diode-array HPLC-UV (Hitachi) and HPLC-MS (Perkin-Elmer, Sciex) to identify the constituents of each of the four sub-libraries

The 4,4'-Dimethoxytrityl-oxymethyl-benzoic acid batch. The DMT protecting group was removed by washing with 4*10 ml 3% dichloroacetic acid in DCM followed by wash with 4*10 ml DCM. The resin was dried and analysed on HPLC (LC-MS) and 6 of the 8 theoretically obtainable balanol analogues were identified.

The 4-nitro-benzoic acid batch. The resin was dried and analysed on HPLC (LC-MS) and 7 of the 8 theoretically obtainable balanol analogues were identified.

The 4-methoxy-benzoic acid batch. The resin was dried and analysed on HPLC (LC-MS) and 7 of the 8 theoretically obtainable balanol analogues were identified.

The 3-fluoro-benzoic acid batch. The resin was dried and analysed on HPLC (LC-MS) and 7 of 8 theoretically obtainable balanol analogues.

In the sub-libraries above, i.e. the 4,4'-Dimethoxytrityl-oxymethyl-benzoic acid batch, the 4-nitro-benzoic acid batch, the 4-methoxy-benzoic acid batch, and the 3-fluoro-benzoic acid batch, 6, 7, 7, and 7 balanol-structures, respectively, were identified as distinct peaks in the LC-UV/MS analyses. The remaining five balanol analogues containing either one of the isomeric building blocks 1-amino-propan-2-ol or 3-amino-propan-1-ol were not observed in the analysis of the library. Several reasons can be proposed to account for this observation where precipitation of individual library members or co-elution in HPLC are very likely possibilities.

CLAIMS

1. A method for the preparation of a compound of the following general formula I:

$$K\text{-}C(=O)\text{-}A\text{-}C(=O)\text{-}L^1\text{-}B\text{-}L^2\text{-}C(=O)\text{-}D \qquad I$$

wherein

K-C(=O)- designates a carboxy group or a derivative thereof;

each of A and B designates an organic biradical;

each of L^1 and L^2 independently designates $-NR^5-$ or -O-, wherein each R^5 independently is selected from hydrogen, optionally substituted C_{1-20}-alkyl, optionally substituted C_{1-20}-alkenyl, optionally substituted C_{1-20}-alkadienyl, optionally substituted C_{1-20}-alkatrienyl, optionally substituted aryl, and optionally substituted heteroaryl, or R^5 designates an additional bond to B (whereby B becomes a triradical);

D designates optionally substituted aryl or optionally substituted heteroaryl;

comprising the following steps

(A) providing an optionally functional group protected moiety -C(=O)-A-C(=O)-M^1 immobilised to a solid support material, wherein -C(=O)-M^1 designates a carboxy group or a derivative thereof;

(B) coupling an optionally functional group protected difunctional entity L'^1-B-L'^2 to the -C(=O)-M^1 end of the immobilised moiety -C(=O)-A-C(=O)-M^1 for the formation of an optionally functional group protected immobilised fragment -C(=O)-A-C(=O)-L^1-B-L'^2;

(C) coupling an optionally functional group protected entity D-C(=O)-M^2, wherein C(=O)-M^2 designates a carboxy group or a derivative thereof, to the L'^2 end of the immobilised fragment -C(=O)-A-C(=O)-L^1-B-L'^2 for the formation of an optionally functional group protected immobilised compound -C(=O)-A-C(=O)-L^1-B-L^2-C(=O)-D, the step optionally including deprotection of any protection group involved in L'^2; and

(D) cleaving the compound K-C(=O)-A-C(=O)-L^1-B-L^2-C(=O)-D from the solid support material, the step optionally including deprotection of one or more functional group(s) attached to A, B, and/or D.

2. A method according to claim 1, wherein the organic biradical -C(=O)-A-C(=O)- is an aliphatic biradical of the formula

$$-C(=O)-(CR^3R^4)_n-C(=O)-$$

wherein n is 1-20, preferably 1-12, in particular 2-8, and

where each of R^3 and R^4 independently is selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted C_{4-8}-alkadienyl, optionally substituted C_{6-8}-alkatrienyl, hydroxy, oxo (thereby forming a keto or aldehyde functionality), -O-R^6, formyl, -C(=O)-R^6, -O-C(=O)-R^6, carboxy, -C(=O)-O-R^6, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted aryl, optionally substituted aryloxy, halogen such as fluoro, chloro, bromo, and iodo, nitro, cyano, -$N(R^5)_2$, -$N(R^7)$-CO-R^6, carbamoyl, mono- or di(C_{1-6}-alkyl)aminocarbonyl, sulphanyl, optionally substituted C_{1-6}-alkylthio, optionally substituted C_{1-6}-alkylthio-C_{1-6}-alkyl, (optionally substituted aryl)thio, guanidino, sulphono ($-SO_3H$), sulphino ($-SO_2H$), halosulphonyl, -$OS(O)_m$-R^6 where m is 2 or 3, -$N(R^7)S(O)_m$-R^6 where m is 2 or 3, -$S(O)_m$-$N(R^7)_2$ where m is 2 or 3, -$S(O)_m$-$NH(R^7)$ where m is 2 or 3, -$S(O)_m$-NH_2 where m is 2 or 3, isocyano, isothiocyano, thiocyano, -$OP(O)_p(R^6)_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5, and -$N(R^7)P(O)_p(R^6)_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5; wherein each R^5 and each R^6 independently is selected from hydrogen, optionally substituted C_{1-20}-alkyl, optionally substituted C_{2-20}-alkenyl, optionally substituted C_{4-20}-alkadienyl, optionally substituted C_{6-20}-alkatrienyl, optionally substituted aryl, and optionally substituted heteroaryl; and each R^7 is selected from hydrogen and C_{1-4}-alkyl; where at the most 5, preferably at the most 3, of the substituents R^3 and R^4 are different from hydrogen; or

a biradical as illustrated in Figure 1 and 2, wherein X is selected from the group consisting of >NR^5, >NH, -O-, -S-, -Se-, -Te-, -CR^1R^2-, >C=O, >C=S, and Y^1, Y^2, R^1, and R^2 each independently designate substituents as defined as optional substituent for aryl and heteroaryl (see above); or Y^1 together with Y^2 may form a biradical which together with the atoms located between these substituents, form(s) a 4-, 5-, 6-, 7- or 8-membered ring which may be an optionally substituted non-aromatic carbocyclic or heteroaromatic ring or an optionally substituted aromatic or heteroaromatic rings; and each Z^1 and Z^2 independently designates =N-, =N^+R^5-.

3. A method according to claim 1 or 2, wherein the organic biradical -L^1-B-L^2- is an aliphatic biradical of the formula

$$-L^1-(CR^3R^4)_n-L^2-$$

where L^1, L^2, R^3, R^4 and n are as defined in claims 1 and 2; or

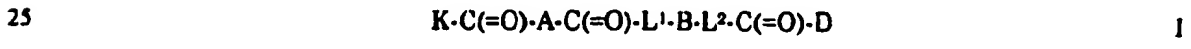
an aliphatic or aromatic amino alcohol as illustrated in Figure 3, wherein X is selected from the group consisting of >NR^6, >NH, -O-, -S-, -Se-, -Te-, -CR^{1}R^2-, >C=O, >C=S, and Y^1, Y^2, R^1, and R^2 each independently designates optional substituents; or Y^1 together with Y^2 may form a biradical which together with the atoms located between these substituents, form(s) a 4-, 5-, 6-, 7- or 8-membered ring which may be an optionally substituted non-aromatic carbocyclic or heteroaromatic ring or an optionally substituted aromatic or heteroaromatic rings; and each Z^1 and Z^2 independently designates =N-, =N$^+$R^5-.

4. A method according to any of the preceding claims wherein one of L^1 and L^2 designates -O- and the other designates -NR^5-, wherein R^5 designates hydrogen, C$_{1-4}$-alkyl or an additional bond to B.

5. A method according to any of the preceding claims, wherein K designates OH, O$^-$, OR'', NH_2, NHR, or NRR', in particular OH, methoxy, or NH_2, where R and R' are selected from C$_{1-6}$-alkyl and benzyl, and R'' is selected from C$_{1-6}$-alkyl, C$_{2-6}$-alkenyl, phenyl, and benzyl.

6. A method according to any of the preceding claims, further comprising a step (E) performed after the step (D), where the step (E) comprises conversion of one compound of the general formula I to another compound of the general formula I.

7. A method for the preparation of a multi-dimensional array of compounds, {A}-{B}-{D}, consisting of at least four compounds each having the general formula I



K-C(=O)-A-C(=O)-L^1-B-L^2-C(=O)-D I

wherein

K-C(=O)- designates a carboxy group or a derivative thereof;

each of A and B designates an organic biradical;

each of L^1 and L^2 independently designates -NR^5- or -O-, wherein each R^5 independently is selected from hydrogen, optionally substituted C$_{1-20}$-alkyl, optionally substituted C$_{1-20}$-alkenyl, optionally substituted C$_{1-20}$-alkadienyl, optionally substituted C$_{1-20}$-alkatrienyl, optionally substituted aryl, and optionally substituted heteroaryl, or R^5 designates an additional bond to B (whereby B becomes a triradical);

D designates optionally substituted aryl or optionally substituted heteroaryl;

comprising

(A) providing an array {A} of m optionally functional group protected moieties -C(=O)-A-C(=O)-M^1 immobilised to a solid support material, wherein -C(=O)-M^1 designates a carboxy group or a derivative thereof;

(B) coupling an array {B} of n optionally functional group protected difunctional entities L'^1-B-L'^2 to the -C(=O)-M^1 end of the immobilised moieties -C(=O)-A-C(=O)-M^1 for the formation of an array {A}-{B} of m·n optionally functional group protected immobilised fragments -C(=O)-A-C(=O)-L^1-B-L'^2;

(C) coupling an array {D} of o optionally functional group protected entities D-C(=O)-M^2, wherein -C(=O)-M^2 designates a carboxy group or a derivative thereof, to the L'^2 end of the immobilised fragments -C(=O)-A-C(=O)-L^1-B-L'^2 for the formation of an array {A}-{B}-{D} of m·n·o optionally functional group protected immobilised compounds -C(=O)-A-C(=O)-L^1-B-L^2-C(=O)-D, the step optionally including deprotection of any protection group involved in L'^2; and

(D) cleaving the array {A}-{B}-{D} of compounds K-C(=O)-A-C(=O)-L^1-B-L^2-C(=O)-D from the solid support material, the step optionally including deprotection of one or more functional group(s) attached to individual As, Bs, and/or Ds;

with the proviso that m·n·o is at least 4, preferably in the range of 6-200, more preferably in the range of 6-100, in particular in the range of 8-64.

8. A method according to claim 7, wherein the organic biradical -C(=O)-A-C(=O)- is as defined in claim 2.

9. A method according to claim 7 or 8, wherein the organic biradical -L^1-B-L^2- is as defined in claim 3.

10. A method according to any of the claims 7-9, wherein one of L^1 and L^2 designates -O- and the other designates -NR^5-, wherein R^5 designates hydrogen, C_{1-4}-alkyl or an additional bond to B.

11. A method according to any of the claims 7-10, wherein K designates OH, O^-, OR'', NH_2, NHR, or NRR', in particular OH, methoxy, or NH_2, where R and R' are selected from C_{1-6}-alkyl and benzyl, and R'' is selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, phenyl, and benzyl.

12. A method according to any of the claims 7-11, further comprising a step (E) performed after the step (D), where the step (E) comprises conversion of at least some of the compounds in the array of compounds of the general formula I to ther compounds of the general f rmula I.

13. The use of an array of compounds according to any of the claims 7-13 for screening purposes.

14. The use of a compound prepared according to a methods defined in any of the claims 1-6 or 7-13 as a medicament.

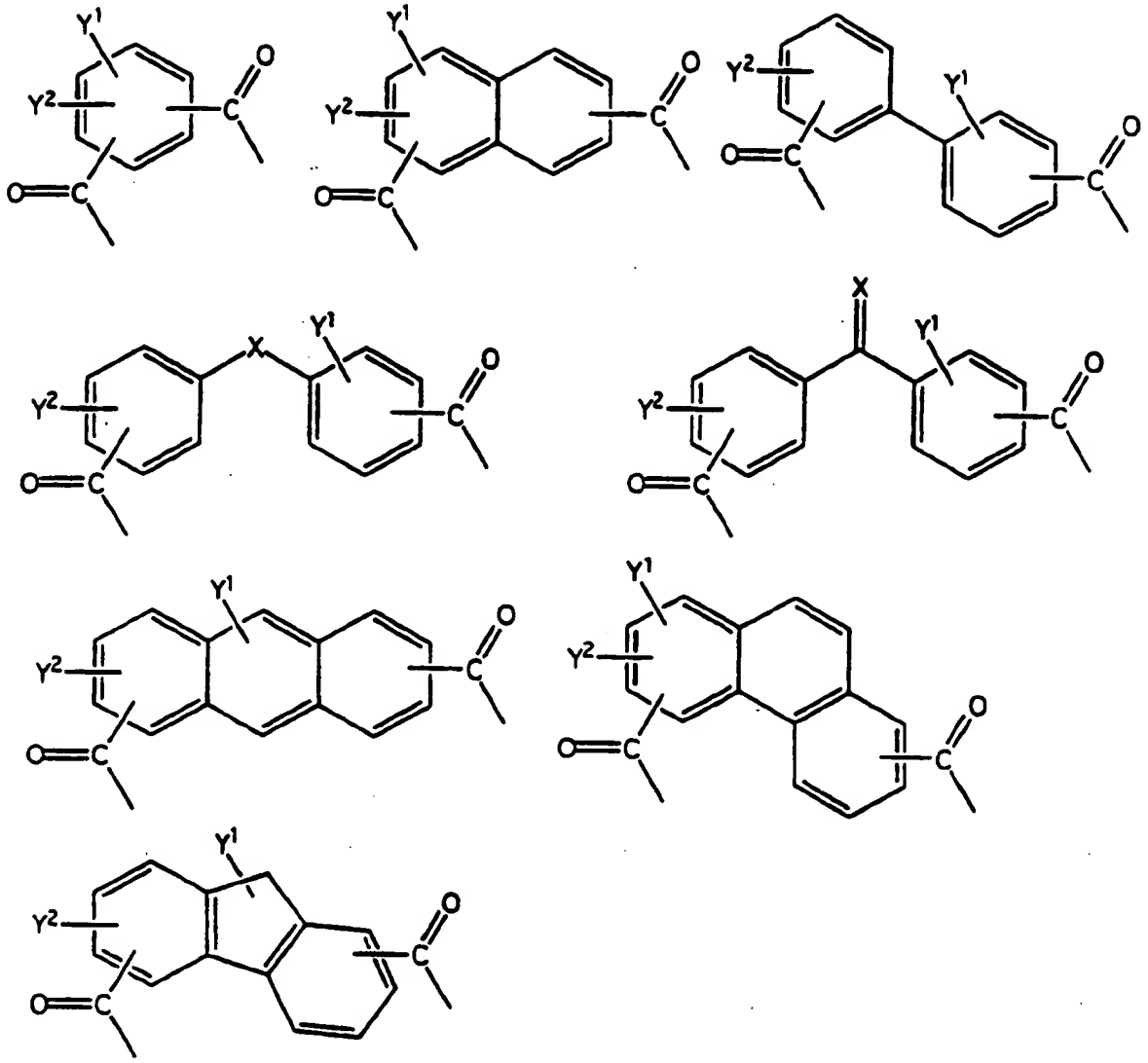


Figure 1

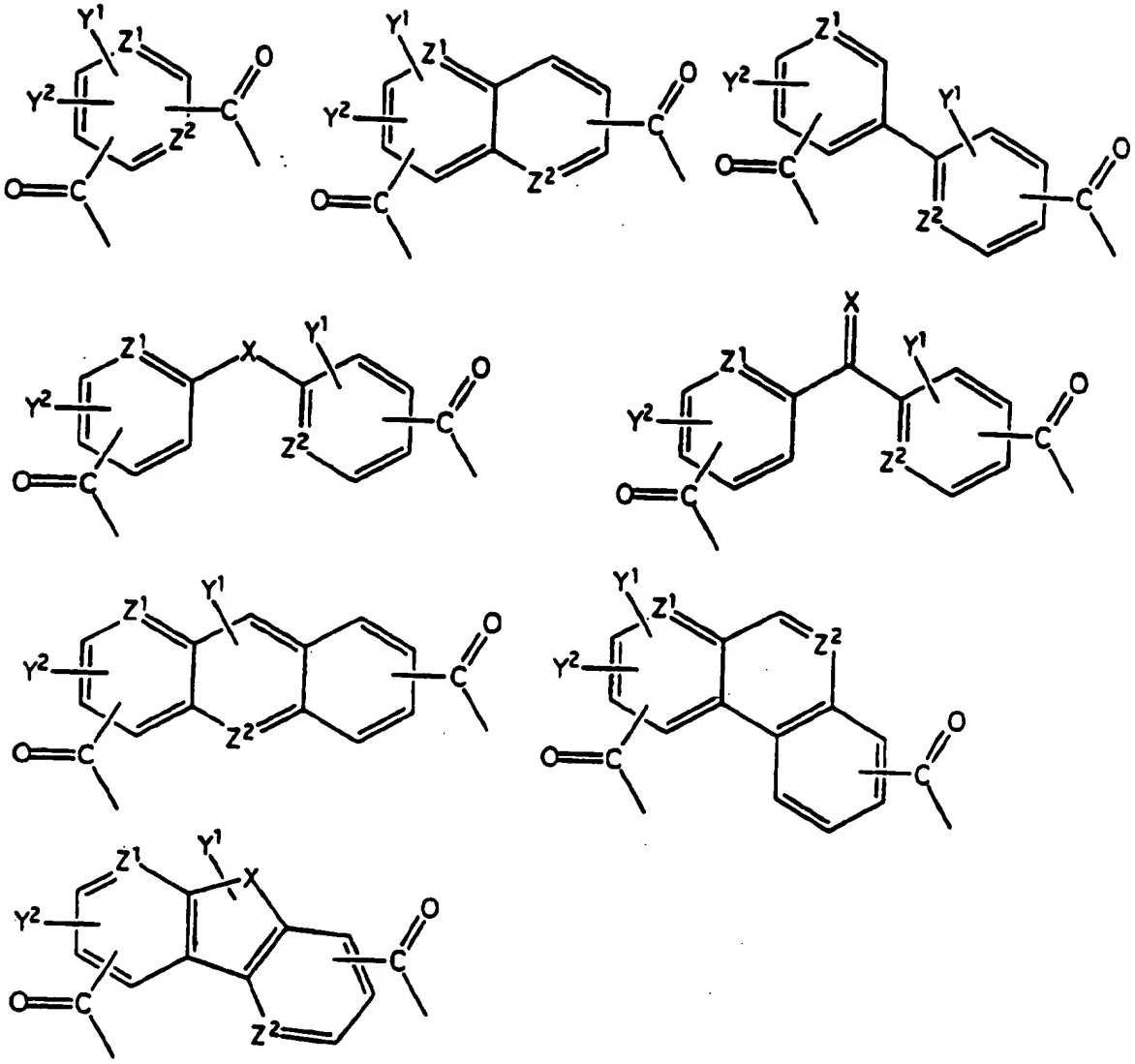


Figure 2

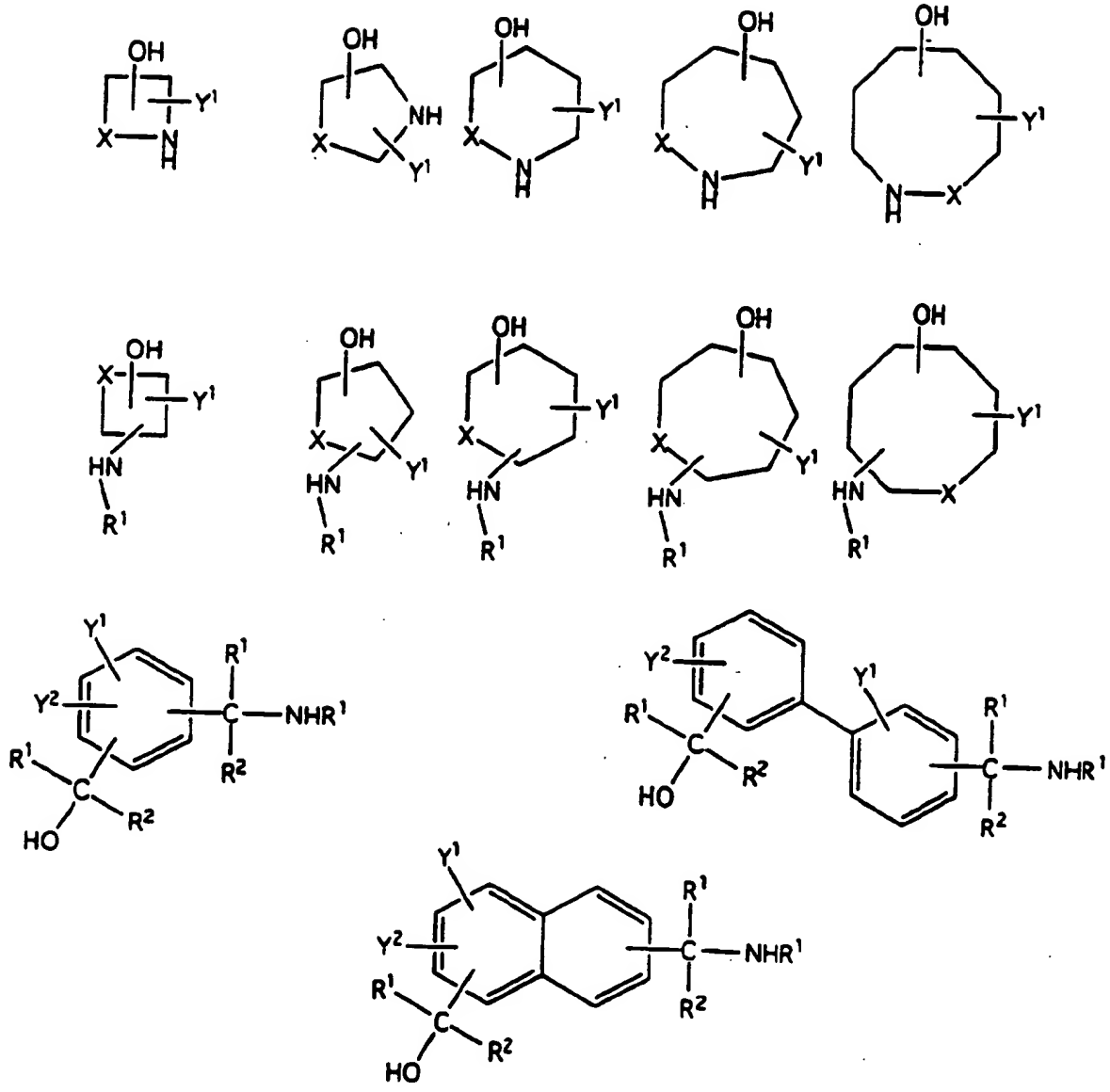


Figure 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00058

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 223/12, A61K 31/55, C07B 61/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Tetrahedron Letters, Volume 37, No 46, 1996, John Nielsen et al, "Combinatorial Solid-Phase Synthesis of Balanol Analogues" page 8439 - page 8442 --	1-14
X	Chem. Eur. J., Volume 1, 1995, K.C. Nicolaou et al, "Total Synthesis of Balanol and Designed Analogues" page 454 - page 466 --	1-14
P,X	Bioorganic & Medicinal Chemistry Letters, Volume 6, No 15, 1996, G. Erik Jagdmann, Jr. et al, "Potent and Selective PKC Inhibitory 5-Membered Ring Analogs of Balanol with Replacement of the Carboxamide Moiety" page 1759 - page 1764 --	1-14

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 May 1997	12.05.1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anna Sjölund Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00058

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Bioorganic & Medicinal Chemistry Letters, Volume 5, No 18, 1995, Yen-Shi Lai et al, "Heteroatom effect in the PKC Inhibitory Activities of Perhydroazepine Analogs of Balanol" page 2147 - page 2150	1-14
X	Bioorganic & Medicinal Chemistry Letters, Volume 5, No 19, 1995, José S. Mendoza et al, "Synthesis and Biological Evaluation of Conformationally Constrained Bicyclic and Tricyclic Balanol Analogues as Inhibitors of Protein Kinase C" page 2211 - page 2216	1-14
X	Bioorganic & Medicinal Chemistry Letters, Volume 5, No 18, 1995, Yen-Shi Lai et al, "Synthesis and PKC Inhibitory Activities of Balanol Analogs with a Cyclopentane Substructure" page 2155 - page 2160	1-14
X	Bioorganic & Medicinal Chemistry Letters, Volume 5, No 17, 1995, G. Erik Jagdmann Jr. et al, "Novel PKC Inhibitory Analogs of Balanol with Replacement of the Ester Functionality" page 2015 - page 2020	1-14
A	WO 9303730 A1 (SPHINX PHARMACEUTICALS CORPORATION), 4 March 1993 (04.03.93)	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00058

Box I Observations where certain claims were found unsearchable (Continuation f Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,2,7
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims searched incompletely: 1,2,7 (the expressions "opt. subst: heteroaryl, aryl, heteroaryloxy" are not clear and concise as prescribed in PCT Art 6. The definition of R3 in claim 1 is unclear as it is not defined in the formula).

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/04/97

International application N .
PCT/DK 97/00058

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9303730 A1	04/03/93	AU 2504192 A	16/03/93
		CA 2115994 A	04/03/93
		EP 0664706 A	02/08/95
		JP 6510280 T	17/11/94